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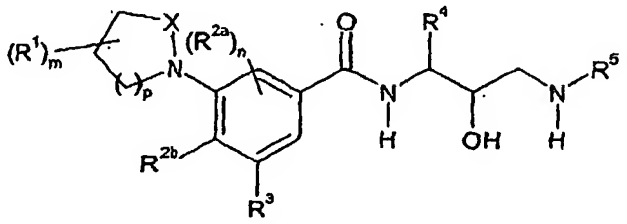
(54) Title: HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(I)

(57) Abstract: The present invention relates to novel hydroxyethylamine compounds of formula (I): (I) having Asp2 (-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated - amyloid levels or -amyloid deposits, particularly Alzheimer's disease.

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HYDROXYETHYLAMINE DERIVATIVES FOR THE TREATMENT OF ALZHEIMER'S DISEASE

The present invention relates to novel hydroxyethylamine compounds having Asp2 (β-secretase, BACE1 or Memapsin) inhibitory activity, processes for their preparation, to compositions containing them and to their use in the treatment of diseases characterised by elevated β- amyloid levels or β-amyloid deposits, particularly Alzheimer's disease.

Alzheimer's disease is a degenerative brain disorder in which extracellular deposition of Aβ in the form of senile plaques represents a key pathological hallmark of the disease (Selkoe, D. J. (2001) Physiological Reviews **81**: 741-766). The presence of senile plaques is accompanied by a prominent inflammatory response and neuronal loss. β-amyloid (Aβ) exists in soluble and insoluble, fibrillar forms and a specific fibrillar form has been identified as the predominant neurotoxic species (Vassar, R. and Citron, M. (2000) Neuron **27**: 419-422). In addition it has been reported that dementia correlates more closely with the levels of soluble amyloid rather than plaque burden (Naslund, J. *et al.* (2000) J. Am. Med. Assoc. **12**: 1571-1577; Younkin, S. (2001) Nat. Med. **1**: 8-19). Aβ is known to be produced through the cleavage of the beta amyloid precursor protein (also known as APP) by an aspartyl protease enzyme known as Asp2 (also known as β-secretase, BACE1 or Memapsin) (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472).

Therefore, it has been proposed that inhibition of the Asp2 enzyme would reduce the level of APP processing and consequently reduce the levels of Aβ peptides found within the brain. Therefore, it is also thought that inhibition of the Asp2 enzyme would be an effective therapeutic target in the treatment of Alzheimer's disease.

APP is cleaved by a variety of proteolytic enzymes (De Strooper, B. and Konig, G. (1999) Nature **402**: 471-472). The key enzymes in the amyloidogenic pathway are Asp2 (β-secretase) and γ-secretase both of which are aspartic proteinases and cleavage of APP by these enzymes generates Aβ. The non-amyloidogenic, α-secretase pathway, which precludes Aβ formation, has been shown to be catalysed by a number of proteinases, the best candidate being ADAM10, a disintegrin and metalloproteinase. Asp1 has been claimed to show both α- and β-secretase activity *in vitro*. The pattern of expression of Asp1 and Asp2 are quite different, Asp2 is most highly expressed in the pancreas and brain while Asp1 expression occurs in many other peripheral tissues. The Asp2 knockout mouse indicates that lack of Asp2 abolished Aβ production and also shows that in this animal model endogenous Asp1 cannot substitute for the Asp2 deficiency (Luo, Y. *et al.* (2001) Nat Neurosci. **4**: 231-232; Cai, H. *et. al.* (2001) Nat Neurosci. **4**: 233-234; Roberds, S. L. *et al.* (2001) Hum. Mol. Genet. **10**: 1317-1324).

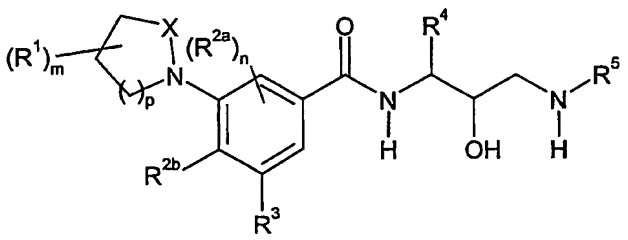
For an agent to be therapeutically useful in the treatment of Alzheimer's disease it is preferable that said agent is a potent inhibitor of the Asp2 enzyme, but should ideally also be selective for Asp2 over other enzymes of the aspartyl proteinase family, e.g Cathepsin D

(Connor, G. E. (1998) Cathepsin D in Handbook of Proteolytic Enzymes, Barrett, A. J., Rawlings, N. D., & Woesner, J. F. (Eds) Academic Press London. pp828-836).

WO 01/70672, WO 02/02512, WO 02/02505, WO 02/02506 and WO 03/040096 (Elan Pharmaceuticals Inc.) describe a series of hydroxyethylamine compounds having β-secretase activity which are implicated to be useful in the treatment of Alzheimer's disease.

We have found a novel series of compounds which are potent inhibitors of the Asp2 enzyme, thereby indicating the potential for these compounds to be effective in the treatment of Alzheimer's disease.

Thus, according to a first aspect of the present invention we provide a compound of formula (I):



(I)

wherein

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^{2a} represents hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

m and n independently represent 0, 1 or 2;

X represents CO, SO or SO_2;

p represents an integer from 1 to 3;

R^{2b} represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^3 represents halogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, cyano, azido, nitro, –NR^7R^8, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -$C{\equiv}CR^{16}$, -C_{1-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 and R^{2b} together with the phenyl group to which they are attached form a naphthyl or benzofused heterocyclic or heteroaryl ring optionally substituted by one or two C_{1-6} alkyl groups;

R^4 represents –C_{2-6} alkynyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-10} cycloalkyl, -C_{3-10} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-C_{1-10} alkyl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -C_{3-10} cycloalkyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl or -CO-C_{1-6} alkyl;
R^{11}, R^{12}, R^a, R^c, R^e and R^f independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;
R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl;
q represents 1 to 3;
wherein said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{3-8} cycloalkyl, amino, cyano or hydroxy groups;
and wherein said cycloalkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, haloC_{1-6} alkyl, -OCF_3, oxo, C_{1-6} alkoxy, -C_{1-6} alkoxy-CN, amino, cyano, nitro, -$NR^{22}COR^{23}$, -$CONR^{22}R^{23}$, -$COOR^{22}$, -SO_2R^{22}, -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-C_{1-6} alkoxy, -C_{1-6} alkanol or hydroxy groups;
or a pharmaceutically acceptable salt or solvate thereof.

In one particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein:
X represents CO or SO_2; and
R^{2a} represents hydrogen, C_{1-3} alkyl or halogen; and
R^3 and R^{2b} together with the phenyl group which they are attached form an unsubstituted benzofused heterocyclic or heteroaryl ring; and
R^4 represents -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl; and
R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-8} cycloalkyl, -C_{3-8} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-8} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl; and
said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkoxy, amino, cyano or hydroxy groups; and
wherein said aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, halogen, -OCF_3, oxo, C_{1-6} alkoxy, amino, cyano, nitro, -$NR^{22}COR^{23}$, -C_{1-6} alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), -C_{1-6} alkyl-C_{1-6} alkoxy, -C_{1-6} alkanol or hydroxy groups.

References to alkyl include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl. It will be appreciated that references to alkenyl and alkenoxy shall be interpreted similarly. It will also be appreciated that when an alkenyl or alkenoxy group is attached to an O, N or S atom the double bond is not at the alpha position relative to said O, N or S atom.

References to cycloalkyl include references to all alicyclic (including branched) isomers of the corresponding alkyl. When a cycloalkyl group is substituted by two or more C_{1-6} alkyl groups,

said cycloalkyl groups together with any two alkyl groups may form a bridged cycloalkyl group which includes bicycloheptyl, adamantyl, bicyclo-octyl and the like.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-8} cycloalkyl fused to a phenyl ring, such as dihydroindenyl or tetrahydronaphthalenyl).

References to 'heteroaryl' include references to mono- and bicyclic heterocyclic aromatic rings containing 1-4 hetero atoms selected from nitrogen, oxygen and sulphur. Examples of monocyclic heterocyclic aromatic rings include e.g. thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl, tetrazolyl and the like. Examples of bicyclic heterocyclic aromatic rings include eg. quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

References to 'heterocyclyl' include references to a 5-7 membered non-aromatic monocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen. Examples of heterocyclic non-aromatic rings include e.g. morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, dioxolanyl, oxathiolanyl, imidazolidinyl, pyrazolidinyl and the like.

References to 'benzofused heterocyclyl or heteroaryl ring' include quinolinyl, isoquinolinyl, indolyl, indazolyl, dihydroindolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl, dihydrochromene, benzotriazolyl, tetrahydroquinoxalinyl and the like.

Preferably, m is 0 or 1, preferably 0. When m represents 1, R^1 is preferably aryl (eg. phenyl).

Preferably, n is 0 or 1, more preferably 1.

When n represents 1, R^{2a} is preferably C_{1-3} alkoxy (eg. methoxy) or halogen (eg. fluorine), more preferably halogen (eg. fluorine).

When n represents 1, R^{2a} is preferably in the ortho position of the phenyl ring.

When X represents SO_2, p is preferably 2 or 3, more preferably 2 and when X represents CO, p is preferably 1 or 2, more preferably 1.

Preferably, R^{2b} is :

hydrogen;

halogen (eg. chlorine or fluorine);

C_{1-6} alkyl (eg. methyl);
C_{1-6} alkoxy (eg. methoxy); or
heterocyclyl (eg. pyrrolidinyl) optionally substituted by an oxo group (eg. 2-oxopyrrolidin-1-yl).

More preferably, R^{2b} is hydrogen or halogen (eg. fluorine), most preferably hydrogen.

Preferably, R^3 represents:
C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl) optionally substituted by one or more (eg. 1, 2 or 3) hydroxy, halogen (eg. fluorine) or C_{1-6} alkoxy groups (eg. methoxy or ethoxy);
C_{2-6} alkenyl (eg. propenyl);
C_{3-8} cycloalkyl (eg. cyclopentyl or cyclohexyl);
cyano;
heterocyclyl (eg. piperidinyl, pyrrolidinyl or isothiazolidinyl) optionally substituted by one or two oxo groups;
$-NR^7R^8$;
$-OR^{13}$;
$-SR^{15}$; or
$-CONR^{17}R^{18}$.

Also preferably, R^3 and R^{2b} together with the phenyl group which they are attached represent indolyl, indazolyl, dihydroindolyl, benzofuranyl, dihydrochromenyl, benzotriazolyl, benzimidazolyl or tetrahydroquinoxalinyl, optionally substituted by one or two C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl or pentyl) groups. More preferably R^3 and R^{2b} together with the phenyl group which they are attached represent benzimidazolyl or indolyl substituted by a C_{1-6} alkyl group (eg. ethyl).

More preferably, R^3 represents:
C_{1-6} alkyl (eg. n-propyl);
$-NR^7R^8$;
C_{3-8} cycloalkyl (eg. cyclopentyl or cyclohexyl);
$-OR^{13}$; or
$-CONR^{17}R^{18}$.

Preferably, R^7 and R^8 independently represent:
hydrogen;
C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, i-propyl, i-butyl, $-CH_2C(CH_3)_3$, $-CH(CH_2CH_3)CH_2CH_3$ or $-(CH_2)_2CH(CH_3)_2$);
C_{3-8} cycloalkyl (eg. cyclopentyl or cyclohexyl);
aryl (eg. phenyl);
$-C_{1-6}$ alkyl-C_{3-8} cycloalkyl (eg. $-CH_2$-cyclopropyl);
$-C_{1-6}$ alkyl-aryl (eg. $-CH_2$-phenyl or $-(CH_2)_2$-phenyl); or

-CO-C_{1-6} alkyl (eg. –$COCH_3$).

More preferably, R^7 represents hydrogen and R^8 represents C_{1-6} alkyl (particularly ethyl or isopropyl, especially ethyl).

Preferably, R^{13} represents C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl or pentyl) optionally substituted by a hydroxy or C_{1-6} alkoxy (eg. methoxy) group, more preferably R^{13} represents ethyl or i-propyl.

Preferably, R^{15} represents C_{1-6} alkyl (eg. methyl or ethyl).

Preferably, R^{17} and R^{18} both represent C_{1-6} alkyl (eg. both represent propyl or one represents propyl and the other represents methyl).

Preferably, R^4 represents -C_{1-6} alkyl-aryl (eg. benzyl) or -C_{1-6} alkyl-heteroaryl (eg. –CH_2-pyridinyl, –CH_2-thiazolyl, –CH_2-furanyl, –CH_2-thienyl or –CH_2-pyrazolyl) optionally substituted by one or two halogen atoms (eg. chlorine or fluorine). More preferably, R^4 represents -C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or two halogen atoms (eg. chlorine or fluorine), most preferably R^4 represents unsubstituted benzyl.

Preferably, R^5 represents

-C_{1-10} alkyl (eg. methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy or –$OCH_2CH(CH_3)_2$) or C_{2-6} alkenoxy (eg.-$OCH_2C(CH_3)=CH_2$) groups;

-C_{3-10} cycloalkyl (eg. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicycloheptyl, adamantyl or bicyclo-octyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl or propyl) or halogen (eg. fluorine) groups;

-C_{1-6} alkyl-C_{3-10} cycloalkyl (eg. –CH_2-cyclohexyl or –CH_2-cyclopropyl);

-aryl (eg. phenyl, dihydroindenyl or tetrahydronaphthalenyl) optionally substituted by one or more hydroxy or C_{1-6} alkoxy (eg. methoxy) groups;

-C_{1-6} alkyl-aryl (eg. benzyl, -ethyl-phenyl, -ethyl-naphthyl, -propyl-phenyl, -C(H)(Me)-phenyl, -C(H)(Et)-phenyl –C(Me)(Me)-benzyl or –C(Me)(Me)-phenyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), hydroxy, -OCF_3, haloC_{1-6} alkyl (eg. -CH_2CF_3 or -CF_3), C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl), C_{2-6} alkynyl, C_{1-6} alkoxy (eg. methoxy, ethoxy, propoxy, isopropoxy or methylethoxy), cyano, nitro, -$COOR^{22}$ (eg. COOH or COOMe), -SO_2R^{22} (eg. –SO_2Me), -$NR^{22}COR^{23}$ (eg. $NHCOCH_3$), -C_{1-6} alkyl-$NR^{22}R^{23}$ (eg. –$CH_2N(CH_3)_2$), -C_{1-6} alkyl-C_{1-6} alkoxy (eg. -$CH_2OC(CH_3)_3$), -C_{1-6} alkanol (eg. -CH_2OH) or -C_{1-6} alkoxy-CN (eg. OCH_2CN) groups;

-C_{1-6} alkyl-heteroaryl (eg. –CH_2-furanyl, –CH_2-quinolinyl, –CH_2-thiophenyl, –CH_2-indolyl, –CH_2-benzoimidazolyl, –CH_2-imidazolyl, –CH_2-benzofuranyl, –CH_2-thiazolyl, –CH_2-pyridinyl, –CH_2-benzothiazolyl, –CH_2-pyrazolyl, -CH_2-isoxazolyl, -CH_2-oxazolyl, –CH_2-pyrrolyl, –CH_2-dihydrobenzofuranyl, –CH_2-dihydrobenzodioxinyl or –CH_2-dihydrochromenyl) optionally

substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl or propenyl), C_{2-6} alkynyl, halogen (eg. bromine or chlorine), haloC_{1-6} alkyl (eg. fluoroethyl or trifluoroethyl), cyano, C_{1-6} alkoxy (eg. methoxy), -$CONR^{22}R^{23}$ (eg. –CONHMe) or -$COOR^{22}$ (eg. –COOMe) groups;

-heterocyclyl (eg. tetrahydropyranyl or tetrahydrothiopyranyl);

-C_{1-6} alkyl-heterocyclyl (eg. –CH_2-tetrahydropyranyl);

-C_{3-10} cycloalkyl-C_{1-10} alkyl (eg. –cyclobutyl-isopropyl, -cyclobutyl-ethyl, -cyclobutyl-propyl, -cyclopropyl-ethyl, -cyclopropyl-propyl, -cyclopropyl-isopropyl, -cyclopropyl-t-butyl, -cyclopropyl-$CH_2CH(CH_3)_2$, -cyclopropyl-$(CH_2)_2CH(CH_3)_2$, –cyclopropyl-$(CH_2)_2CH(CH_3)_2$ or –cyclopropyl-$(CH_2)_3CH(CH_3)_2$);

-C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl (eg. –cyclopropyl-CH_2-phenyl) optionally substituted by one or more halogen (eg. chlorine) atoms;

-C_{3-10} cycloalkyl-aryl (eg. –cyclopropyl-phenyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), hydroxy, -OCF_3, haloC_{1-6} alkyl (eg. -CH_2CF_3 or -CF_3), C_{1-6} alkyl (eg. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl or t-butyl), C_{2-6} alkenyl (eg. ethenyl), C_{2-6} alkynyl, C_{1-6} alkoxy (eg. methoxy, ethoxy, propoxy, isopropoxy or methylethoxy), cyano, nitro, -$COOR^{22}$ (eg. COOH or COOMe), -SO_2R^{22} (eg. –SO_2Me), -$NR^{22}COR^{23}$ (eg. $NHCOCH_3$), -C_{1-6} alkyl-$NR^{22}R^{23}$ (eg. –$CH_2N(CH_3)_2$), -C_{1-6} alkyl-C_{1-6} alkoxy (eg. -$CH_2OC(CH_3)_3$), -C_{1-6} alkanol (eg. -CH_2OH) or -C_{1-6} alkoxy-CN (eg. OCH_2CN) groups;

-$C(R^aR^b)$-CONH-C_{1-6} alkyl (eg. -$C(R^aR^b)$-CONH-i-butyl);

-$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl (eg. $C(R^cR^d)$-CONH-cyclohexyl);

-C_{1-6} alkyl-S-C_{1-6} alkyl (eg. -propyl-S-methyl or –dimethylethyl-S-isobutyl); or

-C_{1-6} alkyl-NR^eR^f (eg. -dimethylpropyl-NR^eR^f).

More preferably R^5 represents:

-C_{3-10} cycloalkyl (eg. cyclohexyl);

-C_{1-6} alkyl-aryl (eg. benzyl) optionally substituted by one or more halogen (eg. chlorine, bromine or fluorine), -OCF_3 or haloC_{1-6} alkyl (eg. -CF_3) groups;

-C_{1-6} alkyl-heteroaryl (eg. -CH_2-thienyl, –CH_2-pyrazolyl or –CH_2-isoxazolyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl, ethyl, isopropyl, propyl or butyl) or haloC_{1-6} alkyl (eg. CH_2CF_3) groups; or

-heterocyclyl (eg. tetrahydropyranyl).

Preferably, q represents 1 or 2.

Preferably, R^a represents hydrogen or C_{1-6} alkyl (methyl).

Preferably, R^b and R^d independently represent C_{1-6} alkyl (eg. methyl, ethyl, propyl or butyl) or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl (eg. -$CH_2CH_2SO_2CH_3$) optionally substituted by one or more hydroxy groups.

Preferably, R^c represents hydrogen or C_{1-6} alkyl (methyl).

Preferably, R^e and R^f both represent C_{1-6} alkyl (eg. methyl).

Preferred compounds according to the invention includes examples E1-E744 as shown below, or a pharmaceutically acceptable salt thereof.

More preferred compounds according to the invention include:
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (1:1) ;
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) ;
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-[(1-methylethyl)amino]benzamide (1:1) ;
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)amino]benzamide (1:1) ;
formic acid - N-((1S,2R)-1-benzyl-3-{[4-fluoro-3-(trifluoromethyl)benzyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) ;
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide ;
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-{[(5-ethyl-3-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) ; and
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino] propyl}benzamide (1:1)
or a pharmaceutically acceptable salt thereof.

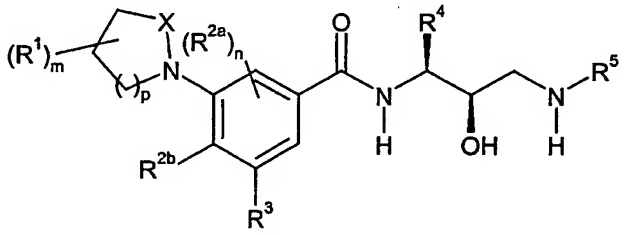
The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, **66**, 1-19, such as acid addition salts formed with inorganic or organic acids e.g. hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, nitrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, p-toluenesulphonates, naphthalenesulphonates, formates or trifluoroacetates. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The present invention also includes within its scope prodrugs of compounds of formula (I). As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery

Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. Preferably, compounds of formula (I) are in the form of a single enantiomer of formula (Ia):

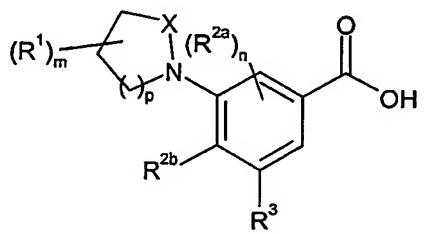


(Ia)

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

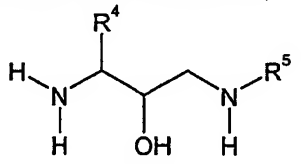
A process according to the invention for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (II)



(II)

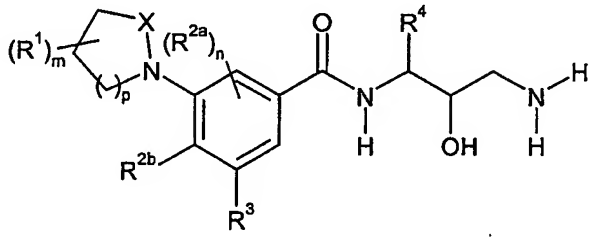
or an activated and optionally protected derivative thereof wherein R^1, m, X, p, R^{2a}, n, R^{2b} and R^3 are as defined above, with a compound of formula (III)



(III)

wherein R^4 and R^5 are as defined above; or

(b) preparing a compound of formula (I) which comprises reductive amination of a compound of formula (IV)



(IV)

wherein R^1, m, X, p, R^{2a}, n, R^{2b}, R^3 and R^4 are as defined above, with an appropriate aldehyde or ketone; or

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion of compounds of formula (I) to other compounds of formula (I).

Process (a) typically comprises the use of water soluble carbodiimide, HOBT and a suitable base such as tertiary alkylamine or pyridine in a suitable solvent such as DMF and at a suitable temperature, eg. between 0°C and room temperature.

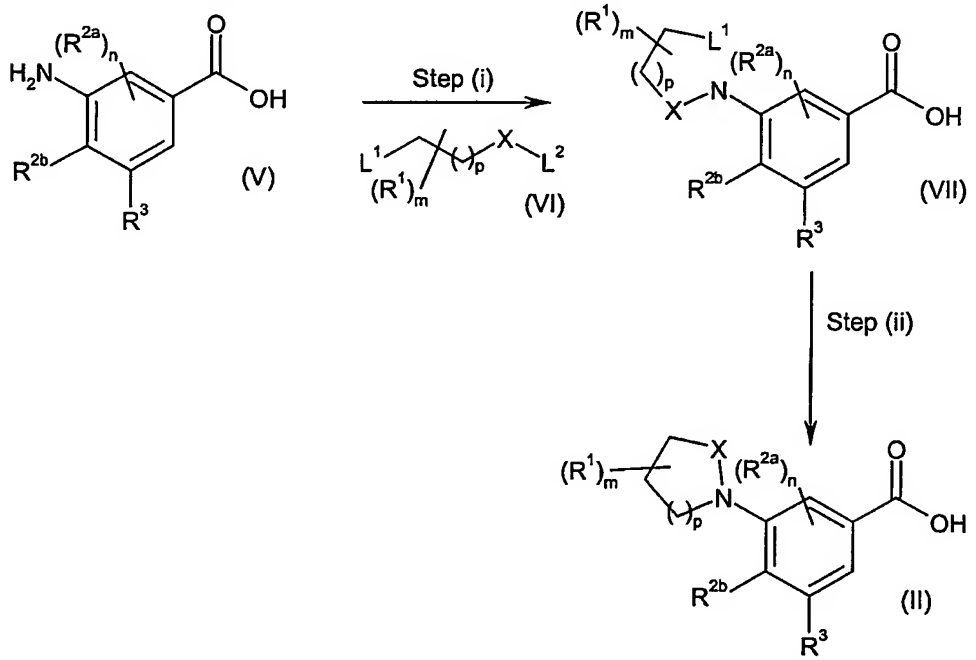
Process (b) typically comprises the use of sodium borohydride triacetate in the presence of a suitable solvent, such as ethanol and dichloromethane and at a suitable temperature, e.g. between 0°C and room temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene and P.G.M. Wuts 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 3rd Ed. 1999). Suitable amine protecting groups include aryl sulphonyl (e.g. tosyl), acyl (e.g. acetyl), carbamoyl (e.g. benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis or hydrogenolysis as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis. Suitable hydroxy protecting groups would be silyl based groups such as t-butyldimethylsilyl, which may be removed using standard methods, for example use of an acid

such as trifluoroacetic or hydrochloric acid or a fluoride source such as tetra n-butylammonium fluoride.

Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, aromatic substitution, ester hydrolysis, amide bond formation or removal and sulphonylation. An example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a C_{2-6} alkenyl containing group to a corresponding compound of formula (I) wherein R^3 represents a C_{1-6} alkyl containing group, using standard hydrogenation or reductive conditions. A further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents - C_{1-6} alkyl-N_3 to a corresponding compound of formula (I) wherein R^3 represents -C_{1-6} alkyl-NH_2, using standard hydrogenation or reductive conditions. A yet further example of such an interconversion reaction may include interconversion of a compound of formula (I) wherein R^3 represents a nitro group to a corresponding compound of formula (I) wherein R^3 represents NH_2, using standard hydrogenation or reductive conditions.

Compounds of formula (II) or activated and optionally protected derivatives thereof may be prepared in accordance with the following process:

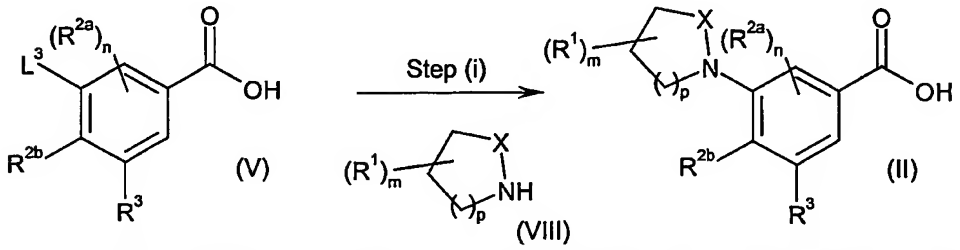


wherein R^{2a}, n, R^{2b}, R^3, p, X, R^1 and m are as defined above and L^1 and L^2 independently represent a suitable leaving group such as a halogen atom (eg. iodine, chlorine or bromine).

Step (i) typically comprises the use of a suitable solvent such as dichloromethane and a suitable base such as triethylamine.

Step (ii) typically comprises the use of sodium hydride in the presence of a suitable solvent such as tetrahydrofuran under nitrogen.

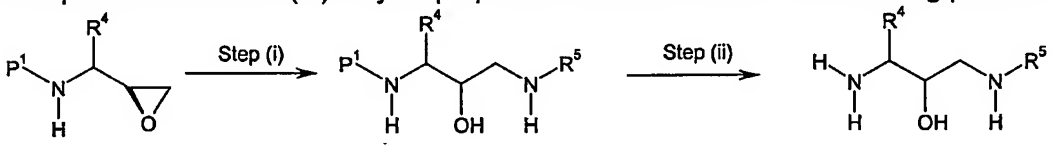
Compounds of formula (II) or activated and optionally protected derivatives thereof may also be prepared in accordance with the following process:



wherein R^{2a}, n, R^{2b}, R^3, p, X, R^1 and m are as defined above and L^3 represents a suitable leaving group such as a halogen atom (eg. iodine, chlorine or bromine).

Step (i) typically comprises the use of caesium carbonate, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene and a suitable catalyst such as tris(dibenzylideneacetone)dipalladium(0) under suitable conditions such as reflux under argon in the presence of a suitable solvent such as dioxan.

Compounds of formula (III) may be prepared in accordance with the following process:

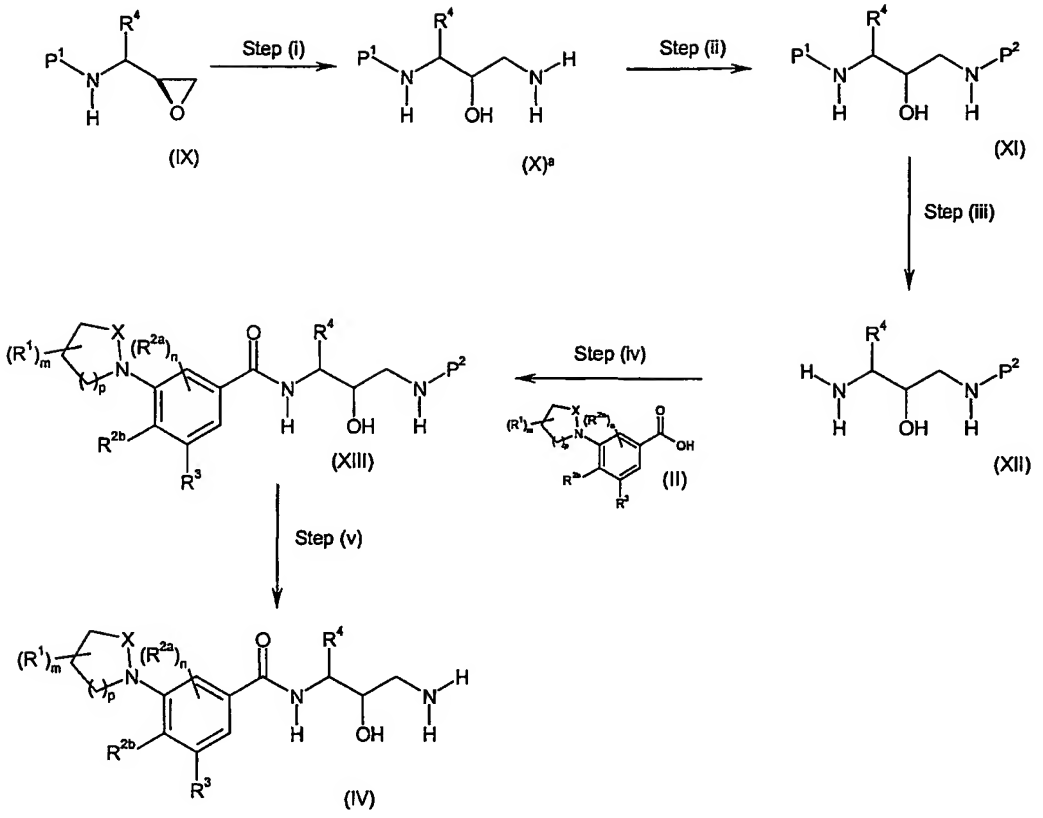


wherein R^4 and R^5 are as defined above and P^1 represents a suitable amine protecting group, such as t-butoxycarbonyl.

Step (i) typically comprises the reaction of a compound of formula (IX) with a compound of formula NH_2R^5 in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

Step (ii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^1 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Compounds of formula (IV) may be prepared in accordance with the following process:



wherein R^1, m, X, p, R^{2a}, n, R^{2b}, R^3, R^4 and P^1 are as defined above and P^2 represents a suitable amine protecting group different to P^1, such as -$COOCH_2$-phenyl.

Step (i) typically comprises the reaction of a compound of formula (IX) in aqueous ammonia in the presence of a suitable solvent, e.g. ethanol at a suitable temperature, e.g. reflux.

When P^2 represents -$COOCH_2$-phenyl, step (ii) typically comprises the use of $ClCOOCH_2$-phenyl in the presence of a suitable base, e.g. triethylamine, a suitable solvent, e.g. dimethylformamide at a suitable temperature, e.g. between 0°C and room temperature.

Step (iii) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^1 represents t-butoxycarbonyl, deprotection typically comprises the use of trifluoroacetic acid in the presence of a suitable solvent, such as dichloromethane at a suitable temperature, e.g. between 0°C and room temperature.

Step (iv) typically comprises reacting a compound of formula (XII) with a compound of formula (II) in the presence of water soluble carbodiimide and HOBT.

Step (iv) typically comprises the use of suitable deprotection reactions as described above for process (c), eg. when P^2 represents -$COOCH_2$-phenyl, deprotection typically comprises the use of a suitable catalyst, eg. palladium in the presence of a suitable solvent, e.g. water and

ethanol and in the presence of a suitable hydrogen source, e.g. ammonium formate at a suitable temperature, eg. 60°C.

Compounds of formula (V) are either commercially available or may be prepared by interconversion of commercially available compounds of formula (V).

Compounds of formula (VI), (VIII) and (IX) are either known or may be prepared in accordance with known procedures.

As a further aspect of the invention there is thus provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical, particularly in the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with diseases characterised by elevated β-amyloid levels or β-amyloid deposits, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

As a further aspect of the invention there is thus provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in the therapy of diseases characterised by elevated β-amyloid levels or β-amyloid deposits, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together, if desirable, with one or more physiologically acceptable diluents or carriers.

It will be appreciated that diseases characterised by elevated β-amyloid levels or β-amyloid deposits include Alzheimer's disease, mild cognitive impairment, Down's syndrome, hereditary cerebral haemorrhage with β-amyloidosis of the Dutch type, cerebral β-amyloid angiopathy

and various types of degenerative dementias, such as those associated with Parkinson's disease, progressive supranuclear palsy, cortical basal degeneration and diffuse Lewis body type of Alzheimer's disease.

Most preferably, the disease characterised by elevated β-amyloid levels or β-amyloid deposits is Alzheimer's disease.

There is also provided a process for preparing such a pharmaceutical formulation which comprises mixing the ingredients.

Compounds of formula (I) may be used in combination with other therapeutic agents. Suitable examples of such other therapeutic agents may be acetylcholine esterase inhibitors (such as tetrahydroaminoacridine, donepezil hydrochloride and rivastigmine), gamma secretase inhibitors, anti-inflammatory agents (such as cyclooxygenase II inhibitors), antioxidants (such as Vitamin E and ginkolidesor), statins or p-glycoprotein (P-gp) inhibitors (such as cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102 and 918).

When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, enteral, parenteral, topical, sublingual, intrathecal or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The

preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.
For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

When the compounds of the invention are administered topically they may be presented as a cream, ointment or patch.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 3000 mg; and such unit doses may be administered more than once a day, for example one, two, three or four times per day (preferably once or twice); and such therapy may extend for a number of weeks, months or years.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Preparation of Intermediates

Description 1

3-Amino-5-nitro-benzoic acid methyl ester (D1)

To a solution of 3-amino-5-nitro-benzoic acid (65 g, 357 mmol, 1 equiv) in MeOH (650 ml) at 0°C was added $SOCl_2$ dropwise (39 ml, 536 mmol, 1.5 equiv). The resulting solution was

allowed to warm to room temperature and stirred for 16 h. A further portion of $SOCl_2$ (10 ml, 137 mmol, 0.4 equiv) was added dropwise and the solution was stirred at room temperature for 5 h, at 50°C for 2 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The solid residue was triturated with AcOEt/*iso*-hexane to give 3-amino-5-nitro-benzoic acid methyl ester (D1) (55 g, 78%) as a pale yellow solid.

Description 2

3-(4-Chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (D2)

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (38 g, 194 mmol, 1 equiv) in CH_2Cl_2 (350 ml) was added NEt_3 (32 ml , 230 mmol, 1.2 equiv) followed by 4-chlorobutyryl chloride (24.7 ml, 220 mmol, 1.13 equiv) dropwise over 20 mn. The resulting mixture was allowed to warm to room temperature and stirred for 30 min. The organic phase was then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and Et_2O to give 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester D2 (56 g, 96%) as a brown solid.

Description 3

3-(5-Chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester (D3)

5-Chlorovaleryl chloride (2.64 g, 17 mmol, 1.1 equiv) in CH_2Cl_2 (5 ml) was added over 2 min to a stirred solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (3 g, 15.3 mmol, 1 equiv) and NEt_3 (2.6 ml, 18 mmol, 1.2 equiv) in CH_2Cl_2 (30 ml). The resulting mixture was stirred for 1 h at room temperature then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give 3-(5-Chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester D3 (6g, 112%) as a brown oil.

Description 4a

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a)

A flask was charged with 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27) (5 g, 19 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 750 mg, 7.5% w/w), NH_4COOH (11.9 g, 190 mmol, 10 equiv) H_2O (30 ml) and MeOH (60 ml). The resulting mixture was stirred at 50°C for 1.5 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue diluted with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give an off white solid. The catalyst was then washed three times with DMF and the combined organic phases concentrated *in vacuo*. The residue was combined with the material obtained previously and was triturated with Et_2O to give amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (3.9 g, 88%) as a white solid which was used in the next step without further purification.

Description 4a (Alternative Procedure)

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (2.2 g, 10 mmol, 1 equiv) in MeOH/Et_2O (1:1, 20 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.3 g, 12 mmol, 1.2 equiv) , DMAP (112 mg, 1 mmol, 0.1 equiv) and the resulting mixture was stirred at room temperature for 16 h then diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (1.6 g, 68%) as a white solid.

Description 4b

3-Amino-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (D4b)

Description 4b was prepared in an analogous manner to Description 4a from 3-nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82).

Description 5

3-Bromo-5-nitro-benzoic acid (D5)

To a solution of 3-amino-5-nitro-benzoic acid (17.6 g, 96.6 mmol, 1 equiv) in 48% aqueous HBr solution (180 ml) at 0°C was added portionwise $NaNO_2$ (8.67 g, 126 mmol, 1.3 equiv) over 20 min. The temperature was kept below 8°C during this addition. The resulting mixture was then added to a suspension of CuBr (9.7 g, 67.6 mmol, 0.7 equiv) in 48% aqueous HBr solution (50 ml) at 65°C over 40 min. The temperature was kept above 60°C during the addition. The resulting mixture was stirred at 70°C for 45 min, cooled to room temperature and diluted with 1L of water. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed twice with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid (D5) (21 g, 88%) as a brown solid. $[M-H]^-$ = 245.7, RT = 2.82 min

Description 6

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6)

To a solution of 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27) (4 g, 16 mmol, 1 equiv) in MeOH/H_2O (9:1, 40 ml) was added 10% palladium on charcoal (50% wet, 800 mg, 0.1 equiv w/w). The resulting mixture was stirred for 6 h at atmospheric pressure under an atmosphere of hydrogen. The catalyst was removed by filtration through a pad of celite and the solvent was removed *in vacuo*. The residue was dried at 60°C under vacuum for 16 h to give 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (3.34 g, 15.2 mmol, 95%) as a pale brown solid. $[M-H]^-$ = 218.8, RT = 1.86 min

Description 7

3-Bromo-5-iodo-benzoic acid (D7)

Description 7 is commercially available from Avocado Research Chemicals Ltd.

Description 8a

3-Bromo-5-iodo-benzoic acid methyl ester (D8a)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (14.6 g, 44.7 mmol, 1 equiv) in MeOH (150 ml) at 0°C was added $SOCl_2$ (3.9 ml, 53.6 mmol, 1.2 equiv). The resulting solution was refluxed for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt and washed twice with 2N aqueous NaOH solution then brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid methyl ester (D8a) (14.8 g, 97%) as a pale brown solid.

Description 8b

3-Bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (50 g, 153 mmol, 1 equiv) in CH_2Cl_2 (500 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (30.8 g, 160 mmol, 1.05 equiv), DMAP (14 g, 114 mmol, 0.75 equiv) and *tert*-butanol (90 ml, 917 mmol, 6 equiv). The resulting mixture was stirred at room temperature for 48 h. DMAP (4.67 g, 38 mmol, 0.25 equiv) was then added and the solution was stirred for another 24 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and washed sequentially with 2N aqueous HCl solution, 1N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (50.6 g, 86%) as a brown solid.

Description 8b (Alternative Procedure)

3-Bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b)

To a solution of 3-bromo-5-iodo-benzoic acid (D7) (50 g, 153 mmol, 1 equiv) in CH_2Cl_2 (500 ml) was added 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (30.8 g, 160 mmol, 1.05 equiv), DMAP (14 g, 114 mmol, 0.75 equiv) and *tert*-butanol (90 ml, 917 mmol, 6 equiv). The resulting mixture was stirred at room temperature for 48 h then DMAP (4.67 g, 38 mmol, 0.25 equiv) was added, and the solution was stirred for another 24 h then concentrated *in vacuo*. The residue was diluted with AcOEt and washed sequentially with 2N aqueous HCl solution, 1N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (50.6 g, 86%) as a brown solid.

Description 9a

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester D9a

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid methyl ester (D8a) (14.8 g, 43.4 mmol, 1 equiv) , Cs_2CO_3 (21 g, 65 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (794 mg, 0.87 mmol, 0.02 equiv), Xantphos (1.5 g, 2.6 mmol, 0.06 equiv) and dioxan (150 ml). Pyrrolidin-2-one (5 ml, 5.54 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at 55°C for 5 days then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 to 1/1) gave 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (6.4 g, 50%) as a white solid. $[M+H]^+$ = 299.9, RT = 2.95 min

Description 9a (Alternative Procedure)

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a)

To a solution of 3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13) (530 mg, 1.6 mmol, 1 equiv) in THF (5 ml) at room temperature was added NaH (60% in mineral oil, 64 mg, 1.7 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 2 h. H_2O was then added and the resulting mixture was diluted with AcOEt. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (361 mg, 76%) as a yellow solid. $[M-H]^-$ = 296.3, RT = 2.49.

Description 9b

3-Bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b)

A flask was charged under nitrogen with bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (11.5 g, 30 mmol, 1 equiv), Cs_2CO_3 (13.7 g, 42 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (549 mg, 0.6 mmol, 0.02 equiv), Xantphos (1.04 g, 1.8 mmol, 0.06 equiv) and dioxan (100 ml). Pyrrolidin-2-one (2.5 ml, 33 mmol, 1.1 equiv) was then added *via syringe* and the resulting mixture was stirred at 60°C for 60 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue which was triturated with Et_2O to give 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) (6.63 g, 65%) as an off white solid. The filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 to 1/1) gave a further 1.46g (14%) of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) as a white solid. $[M+H-t\text{Bu})]^+$ = 285.9, RT = 3.46 min

Description 10

3-Bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (6.42 g, 16.7 mmol, 1 equiv), Cs_2CO_3 (7.6 g, 23.4 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (307 mg, 0.33 mmol, 0.02 equiv), Xantphos (578 mg, 1 mmol, 0.06 equiv) and dioxan (120 ml). δ-Valerolactam (1.9 ml, 20 mmol, 1.2 equiv) was then added *via syringe* and the resulting mixture was stirred at 60°C for 40 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 1/1) gave 3-bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10) (4 g, 68%) as a white solid. RT = 2.88 min

Description 11

3-Bromo-5-nitro-benzoic acid methyl ester (D11)

To a solution of 3-bromo-5-nitro-benzoic acid (D5) (22.3 g, 90.6 mmol, 1 equiv) in MeOH (300 ml) at 0°C was added $SOCl_2$ (7.9 ml, 108 mmol, 1.2 equiv) dropwise. The resulting solution was stirred at reflux for 4 hours then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt, washed twice with 2N aqueous NaOH solution and once with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid methyl ester (D11) (22.1 g, 94%) as a pale brown solid. RT = 3.18 min

Description 11 (Alternative Procedure)

3-Bromo-5-nitro-benzoic acid methyl ester (D11)

To an ice cold solution of 3-bromo-5-nitro-benzoic acid (D5) (2.5 g, 10 mmol, 1 equiv) in MeOH (25 ml) was added $SOCl_2$ (1 ml, 15 mmol, 1.5 equiv) dropwise. The resulting solution was allowed to warm to room temperature and was then stirred at 60°C for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-nitro-benzoic acid methyl ester (D11) (2.6 g, 100%) as a yellow solid. RT = 3.22 min

Description 12

3-Amino-5-bromo-benzoic acid methyl ester (D12)

To a solution of 3-bromo-5-nitro-benzoic acid methyl ester (D11) (12.1 g, 46.5 mmol, 1 equiv) in MeOH (200 ml) was added $SnCl_2$ (44 g, 233 mmol, 5 equiv). The resulting mixture was stirred at reflux for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ice-cold AcOEt and H_2O. The aqueous phase was basified with 2N aqueous NaOH solution until a white precipitate appeared, then slowly with 12.5N aqueous NaOH solution until this precipitate disappeared. The temperature was kept below 10°C during this addition. The two layers were separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-bromo-benzoic acid methyl ester (D12) (9.9 g, 93%) as a brown solid.

Description 13

3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13)

To a solution of 3-amino-5-bromo-benzoic acid methyl ester (D12) (460 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (10 ml) at room temperature was added NEt_3 (306 µl, 2.2 mmol, 1.1 equiv) then 4-chlorobutyrylchloride (247 µl, 2.2 mmol, 1.1 equiv). The resulting mixture was stirred at room temperature for 16 h and then diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(4-chloro-butanoylamino)-benzoic acid methyl ester (D13) (530 mg, 79 %) as a pale yellow oil. RT = 2.88 s

Description 14

3-(3-Chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14)

To a solution of 3-amino-5-nitro-benzoic acid methyl ester (D1) (45 g, 229 mmol, 1 equiv) in CH_2Cl_2 (450 ml) was added pyridine (18.5 ml, 229 mmol, 1 equiv), DMAP (100 mg, 0.8 mmol, catalytic) and 3-chloropropanesulfonyl chloride (28 ml, 230 mmol, 1 equiv). The resulting mixture was stirred for 40 h then diluted with AcOEt. The organic phase was diluted with 2N aqueous HCl solution. The resulting solid was filtered to give 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (23 g, 32%). The filtrate was separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt and *iso*-hexane to give a further 50 g (65%) of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14) as a pale brown solid. $[M-H]^-$ = 334.9, RT = 3.11 min

Description 15

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15)

To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-nitro-benzoic acid methyl ester (D14) (73g, 217 mmol, 1 equiv) in EtOH (600 ml) was added Et_3N (60 ml, 430 mmol, 2 equiv) and the resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and AcOEt to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (58 g, 88%) as a pale brown solid. $[M+H+NH_3]^+$ = 318.0, RT = 2.78 min

Description 15 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15)

A 50 ml flask was charged under nitrogen with 3-bromo-5-nitro-benzoic acid methyl ester (D11) (1 g, 3.8 mmol, 1 equiv), Cs_2CO_3 (536 mg, 4.4 mmol, 1.2 equiv) tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0055 mmol, 0.0154 equiv), Xantphos (10 mg, 0.014 mmol, 0.04 equiv) and toluene (15 ml). Isothiazolidine 1,1-dioxide (D22a) (536 mg, 4.4 mmol, 1.1 equiv) was then added and the resulting mixture was stirred at 90°C for 16 hours then cooled to room temperature and diluted with H_2O and AcOEt. The layers were separated, the aqueous phase diluted with a saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (187 mg, 16%) as a yellow solid. $[M+H+NH_3]^+$ = 318.0,
RT = 2.81 min

Description 16

3-Amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D16)

A flask was charged with 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-nitro-benzoic acid methyl ester (D15) (25 g, 83 mmol, 1 equiv) and 10% palladium (0) on charcoal (50% wet, 5 g, 10% w/w) and EtOH (500 ml). The resulting suspension was stirred under an atmosphere of hydrogen (atmospheric pressure) for 4 h and the catalyst was filtered off through a pad of celite. The catalyst was washed three times with DMF and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in AcOEt and filtered again through celite

in order to remove residual catalyst. The organic phase was concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D16) (18 g, 80%) as a pale brown solid. $[M+H]^+$ = 271.0, RT = 2.16 min

Description 17

3-Bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid *tert*-butyl ester D8b (1 g, 2.6 mmol, 1 equiv), Cs_2CO_3 (1.26 g, 3.9 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.013 mmol, 0.005 equiv), Xantphos (22 mg, 0.038 mmol, 0.015 equiv) and toluene (20 ml). Isothiazolidine 1,1-dioxide (D22a) (350 mg, 2.9 mmol, 1.1 equiv) was then added and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature and diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17) (350 mg 38%) as a white solid.

Description 18

3-bromo-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-benzoic acid *tert*-butyl ester (D18)

Description 18 was prepared in an analogous manner to Description 17b from 3-bromo-5-iodo-benzoic acid *tert*-butyl ester (D8b) (5.2 g, 13.6 mmol) and [1,2] thiazinane 1,1-dioxide (D22b) which gave the title compound (D18) (1.8 g, 34%) as a pale yellow solid.
$[M+H\text{-}tert\text{-}Bu]^+$ = 335.9, RT = 3.26 min

Description 19

3-Bromo-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D19)

To a solution of 3-amino-5-bromo-benzoic acid methyl ester (D12) (2.3 g, 10 mmol, 1 equiv) in CH_2Cl_2 (30 ml) was added pyridine (1.6 ml, 20 mmol, 2 equiv), DMAP (320 mg, 2.5 mmol, 2.5 equiv) and 3-chlorosulphonyl chloride (1.46 ml, 12 mmol, 1.2 equiv) dropwise. The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-bromo-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D19) (3.36 g, 91%) as a red solid.
$[M-H]^-$ = 369.9, RT = 3.25 min

Description 20

4-Chloro-1-butanesulfonyl chloride (D20)

To a mixture of [1,2]oxathiane 2,2-dioxide (D23) (50 g, 367 mmol, 1 equiv) and $SOCl_2$ (29 ml, 401 mmol, 1.1 equiv) was added DMF (4 ml, 51.6 mmol, 0.14 equiv). The resulting mixture was stirred under nitrogen at 70°C for 3 days. A second portion of $SOCl_2$ (10 ml, 137 mmol, 0.37 equiv) was added. The mixture was stirred at 70°C for another 3 days and then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with toluene then

concentrated *in vacuo*. This procedure was repeated and the residue was dried under vacuum for 16 h to give crude 4-chloro-1-butanesulfonyl chloride (D20) (63 g, 90%).

Description 21a

3-Chloro-1-propanesulfonamide (D21a)

To an ice-cooled solution of 3-chloro-1-propanesulfonyl chloride (*Chem. Pharm. Bull*, 40(1),75-84,**1999**) (30 ml, 250 mmol, 1 equiv) in CH_2Cl_2 (150 ml) was slowly added aqueous ammonia solution (32%, 30 ml). The resulting mixture was stirred at room temperature for 16 h and H_2O (20 ml) was added. The layers were separated and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-chloro-1-propanesulfonamide (D21a) (27 g, 69%) as a white solid *Chem. Pharm. Bull*, 40(1),75-84,**1999**].

Description 21b

3-Chloro-1-butanesulfonamide (D21b)

To an ice-cooled solution of 4-chloro-1-butanesulfonyl chloride (D20) (43 g, 225 mmol, 1 equiv) in CH_2Cl_2 (350 ml) was slowly added aqueous ammonia solution (25%, 140 ml). The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was diluted with AcOEt and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-chloro-1-butanesulfonamide (D21b) (31g, 88%).

Description 22a

Isothiazolidine 1,1-dioxide (D22a)

To a solution of 3-chloro-1-propanesulfonamide (D21a) (27 g, 170 mmol, 1 equiv) in EtOH (250 ml) at room temperature was added NaOEt (11.7 g, 170 mmol, 1 equiv). The resulting mixture was refluxed for 5 h then cooled to room temperature and concentrated *in vacuo*. The residual solid was extracted thoroughly with CH_2Cl_2 and the extracts were concentrated *in vacuo* to give isothiazolidine 1,1-dioxide (D22a) (20 g, 100%).

Description 22b

[1,2] Thiazinane 1,1-dioxide (D22b)

To a solution of 3-chloro-1-butanesulfonamide (D21b) (31 g, 200 mmol, 1 equiv) in EtOH (500 ml) at room temperature was added NaOEt (14.9 g, 220 mmol, 1.1 equiv). The resulting mixture was refluxed for 5 h then cooled to room temperature and concentrated *in vacuo*. The residual solid was extracted thoroughly with CH_2Cl_2 and the extracts were concentrated *in vacuo*. The residual solid was triturated with Et_2O to give [1,2]thiazinane 1,1-dioxide (D22b) (18.7 g, 69%) as a pale brown solid.

Description 23

4-chloro-3,5-dinitrobenzoic acid (D23)

Description 23 is commercially available from Sigma-Aldrich Company.

Description 24

4-Methoxy-3,5-dinitro-benzoic acid (D24)

To a solution of KOH (1.12 g, 20 mmol, 1 equiv) in MeOH (20 ml) at 0°C was added portionwise 4-chloro-3,5-dinitrobenzoic acid (D23) (4.93 g, 20 mmol, 1 equiv). The resulting mixture was refluxed for 1 h then cooled to room temperature. A second portion of KOH (1.12 g, 20 mmol, 1 equiv) was added and the mixture refluxed for 90 min, cooled to room temperature and diluted with H_2O. The aqueous phase was acidified to pH 1 and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give crude 4-methoxy-3,5-dinitro-benzoic acid (D24) (4.49 g, 93%) as a light brown solid.

Description 25

4-Methoxy-3,5-dinitro-benzoic acid methyl ester (D25)

To a solution of crude 4-methoxy-3,5-dinitro-benzoic acid (D24) (4.43 g, 17.3 mmol, 1 equiv) in MeOH (60 ml) was added concentrated H_2SO_4 (4 ml). The resulting mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The two layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 85/15) gave 4-methoxy-3,5-dinitro-benzoic acid methyl ester (D25) (2.84 g, 65%) as an off white solid.

The following descriptions were prepared in an analogous manner to Description 25 from commercially available starting materials:

Description	Starting material
4-Chloro-3,5-dinitro-benzoic acid methyl ester (D25a)	D24a
3-Amino-4-chloro-benzoic acid methyl ester (D27c)	D26

Description 27a

3,5-Diamino-4-chloro-benzoic acid methyl ester (D27a)

A mixture of 4-chloro-3,5-dinitro-benzoic acid methyl ester (D25a) (2.6 g, 10 mmol, 1 equiv) and $SnCl_2$ (18.95 g, 100 mmol, 10 equiv) in MeOH (80 ml) was refluxed for 1 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 2N aqueous NaOH solution. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with 1:1 Et_2O/iso-hexane to give 3,5-diamino-4-chloro-benzoic acid methyl ester (D27a) (1.56 g, 78%) as a light orange solid.

The following Description was prepared in an analogous manner to Description 27a (using 5 equivalents of $SnCl_2$ for nitroaryls and 10 equivalents for bis nitroaryls) from the starting material indicated in the below table:

Description	Starting material
3,5-Diamino-4-methoxy-benzoic acid methyl ester (D27b)	D25b

Description 28c

4-Chloro-3-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28c)

4-Chlorobutyryl chloride (2.82 g, 20 mmol, 2.0 equiv) in CH_2Cl_2 (5 ml) was added over 2 min to a stirred solution of 3-amino-4-chloro-benzoic acid methyl ester (D27c) (1.66 g, 10 mmol, 1 equiv) and NEt_3 (2.22 g, 22 mmol, 2.2 equiv) in CH_2Cl_2 (40 ml). The resulting mixture was stirred for 1 h at room temperature then washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with CH_2Cl_2 to give 4-chloro-3-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28c) (1.81 g, 48%) as a pale pink solid.

The following Descriptions were prepared in an analogous manner to the process described in D28c from the starting material indicated in the below table:

Description	Precursor
4-Chloro-3,5-bis-(4-chloro-butanoylamino)-benzoic acid methyl ester (D28a)	D27a
3,5-Bis-(4-chloro-butanoylamino)-4-methoxy-benzoic acid methyl ester (D28b)	D27b

Description 30

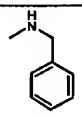
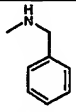
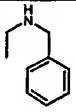
(Benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30)

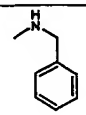
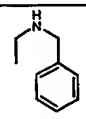
A flask was charged under nitrogen with 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) (4.6 g ,13 mmol, 1 equiv), sodium *tert*-butoxide (1.9 g, 19.5 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (395 mg, 0.65 mmol, 0.05 equiv), 2-(dicyclohexylphosphino)biphenyl (341 mg, 0.97 mmol, 0.075 equiv) and toluene (100 ml). N-Ethylbenzylamine (2.9 ml, 19.5 mmol, 1.5 equiv) was then added via syringe and the resulting mixture was stirred at 90°C for 2 h then cooled to room temperature, diluted with H_2O and AcOEt. The layers were separated, the aqueous phase diluted with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/2) gave (benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30) (3 g, 60%) as a white solid.

$[M+H]^+$ = 395.0, RT = 3.70 min.

Descriptions 31-35 (D31-D35)

Descriptions 31-35 were prepared in an analogous manner to D30 from the appropriate aryl bromide and amine starting materials listed in the below table:

Description	Aryl bromide	Amine	$[M+H]^+$	RT (min)
(Benzyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D31)	D9b		381.1	3.59
(Benzyl-methyl-amino)-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D32)	D10		395.2	3.51
(Benzyl-ethyl-amino)-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D33)	D10			

(Benzyl-methyl-amino)-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D34)	D17		417.1	3.51
(Benzyl-ethyl-amino)-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-benzoic acid *tert*-butyl ester (D35)	D18		445.2	3.82

Description 36

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D6) (280 mg, 1.25 mmol, 1 equiv) in a mixture of 2N aqueous HCl solution (2.5ml) and MeOH (5ml) at 0 °C was added NaN_3 (190 mg, 2.75 mmol, 2.2 equiv) portionwise over 20 min. H_2O (5ml) was added and the resulting mixture was heated at 90°C for 1 h then cooled to room temperature and diluted with AcOEt. The two layers were separated and the aqueous phase was extracted twice with AcOEt (20 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a crude product which was triturated with Et_2O/MeOH to give 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36) (110 mg, 40%) as a light tan solid.

Description 37

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37)

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D36) (400 mg, 1.72 mmol, 1 equiv) was heated at reflux in a mixture of MeOH (20 ml) and concentrated H_2SO_4 (4 drops) for 7 h. The solution was then cooled to room temperature and concentrated *in vacuo* to give of 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (300 mg, 74%) as a light brown solid.

Description 37 (Alternative Procedure)

3-Hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37)

3-Amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (1.50 g, 6.4 mmol, 1 equiv) was dissolved in a mixture of 2N aqueous HCl solution (25 ml) and MeOH (50 ml) at 0 °C and treated portionwise with NaN_3 (950 mg, 13.8 mmol, 2.2 equiv) over 20 min. H_2O (50ml) was added and the resulting mixture was heated at 90 °C for 45 min then cooled to room temperature and diluted with Et_2O (300 ml). The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (1.0 g, 67%) as a tan solid.

Description 38

3-(3-Benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38)

A solution of 3-hydroxy-5-(2-oxopyrrolidin-1-yl)-benzoic acid methyl ester (D37) (300 mg, 1.28 mmol, 1 equiv), 3-benzyloxypropan-1-ol (0.28 ml, 1.79 mmol, 1.4 equiv) and triphenyl phosphine (470 mg, 1.79 mmol, 1.4 equiv) in THF (10 ml) at room temperature was treated dropwise with DEAD (0.282 ml, 1.79 mmol, 1.4 equiv). The mixture was stirred for 16 h at

room temperature then concentrated *in vacuo*. Purification by flash chromatography on silica gel (ethyl acetate/iso-hexane : 1/4 to 1/1) gave 3-(3-benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38).

Description 39

Description 39 was prepared in an analogous manner to Description 38 from Description 37 using the appropriate alcohol indicated in the table below:

Description	Alcohol
3-(2-Benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D39)	

Description 40

3-(2-benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D40)

Description 40 was prepared by saponification of Description 39 in accordance with known procedures.

Description 41

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41)

1-[3-Amino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-phenyl]-propan-1-one (D16) (1.0 g, 3.7 mmol, 1 equiv) dissolved in a mixture of 2N aqueous HCl solution (15 ml) and MeOH (30 ml) was stirred at 0 °C and treated portionwise with sodium nitrite (550 mg, 8.0 mmol, 2.2 equiv) over 20 min. H_2O (50 ml) was added and the resulting mixture was heated at 90 °C for 45 min, cooled, and diluted with Et_2O (300 ml) The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give crude 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (800 mg, 80%) as a brown oil.

Description 41 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41)

A mixture of 3-benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54) (4.5 g, 12.5 mmol, 1 equiv), NH_4COOH (7.7 g, 125 mmol, 10 equiv) and 10% Pd on charcoal (50% wet, 1.0g, 11% w/w) in MeOH (150ml) and H_2O (10 ml) was heated at 50 °C for 2 h. The cooled reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. H_2O (100 ml) was added to the filtrate which was then extracted with AcOEt (150 ml). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallised from Et_2O to yield of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (2.6 g, 77%) as a white solid.

Description 42

5-hydroxy-isophthalic acid dimethyl ester (D42)

Description 42 is commercially available from Sigma-Aldrich Company.

Description 43

5-Ethoxy-isophthalic acid dimethyl ester (D43)

K_2CO_3 (31.6 g, 223 mmol, 2.23 equiv) and iodoethane (17.8 ml, 230 mmol, 2.3 equiv) were added to a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (21 g, 100 mmol, 1 equiv) in acetone (500 ml) at room temperature. The resulting solution was refluxed for 16 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid dimethyl ester (D43) (23 g, 96%) as a white solid. RT = 3.13 min

Description 44

5-Benzyloxy-isophthalic acid dimethyl ester (D44)

K_2CO_3 (21 g, 153 mmol, 2 equiv) and benzyl bromide (11 ml, 92 mmol, 1.2 equiv) were added to a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (16.1g, 76.7 mmol, 1 equiv) in acetone (400 ml) at room temperature. The resulting solution was refluxed for 18 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt. The aqueous phase was extracted with AcOEt and the combined organic layers were washed with 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-benzyloxy-isophthalic acid dimethyl ester (D44) (24.2 g, 105%) as a white solid. $[M+H]^+$ = 301.0, RT = 3.50 min

Description 45

5-Ethoxy-isophthalic acid monomethyl ester (D45)

To a solution of 5-ethoxy-isophthalic acid dimethyl ester (D43) (22 g, 92.4 mmol, 1 equiv) in MeOH (440 ml) was added 1N aqueous NaOH solution (87.8 ml, 87.8 mmol, 0.95 equiv) and the resulting solution was stirred at room temperature for 17 h. Most of the MeOH was removed *in vacuo* and the residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous layer was extracted with AcOEt, acidified to pH 1 and re-extracted with AcOEt. The second organic extract was dried over $MgSO_4$ and concentrated *in vacuo* to give 5-ethoxy-isophthalic acid monomethyl ester (D45) (17 g, 82%) as a white solid. $[M+H+NH_3]^+$ = 242.0, RT = 2.79 min

Description 46

5-Benzyloxy-isophthalic acid monomethyl ester (D46)

To a solution of 5-benzyloxy-isophthalic acid dimethyl ester (D44) (24 g, 80 mmol, 1 equiv) in MeOH (300 ml) was added 1N aqueous NaOH solution (76 ml, 76 mmol, 0.95 equiv) and the resulting solution was stirred at room temperature for 17 h. A second portion of 1N aqueous NaOH solution (15 ml, 15 mmol, 0.2 equiv) was added and the solution stirred for another 6 h. Most of the MeOH was removed *in vacuo* and the residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous layer was extracted with AcOEt, acidified to pH 1 and re-extracted with AcOEt. The second organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-benzyloxy-isophthalic acid monomethyl ester (D46) (15.5 g, 68%) as a white solid. $[M+H]^+$ = 2.86.0, RT = 3.32 min

Description 47

3-Benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47)

NEt_3 (14.2 ml, 102 mmol, 1.3 equiv) and diphenylphosphoryl azide (22 ml, 102 mmol, 1.3 equiv) were added to a suspension of 5-ethoxy-isophthalic acid monomethyl ester (D45) (17.6 g, 78.6 mmol, 1 equiv) in toluene (250 ml) and the mixture heated at 80°C for 3 h. Benzyl alcohol (12 ml, 118 mmol, 1.5 equiv) was added and the resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (300 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47) (15 g, 62%) as a white solid. $[M-H]^-$ = 328.1, RT = 3.46 min

Description 48

3-Benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48)

NEt_3 (8.2 g, 81 mmol, 1.5 equiv) and diphenylphosphoryl azide (22.3 g, 81 mmol, 1.5 equiv) were added to a suspension of 5-benzyloxy-isophthalic acid monomethyl ester (D46) (15.5 g, 54.2 mmol, 1 equiv) in toluene (120 ml) and the resulting mixture heated at 80°C for 3 h. 2-Trimethylsilylethanol (12.7 g, 108 mmol, 2 equiv) was added and the resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O and *iso*-hexane to give 3-benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48) (8.5 g, 40%) as a white solid.

Description 49

3-Amino-5-ethoxy-benzoic acid methyl ester (D49)

A mixture of 3-benzyloxycarbonylamino-5-ethoxy-benzoic acid methyl ester (D47) (15 g, 45.5 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 1.5 g, 5% w/w) and NH_4COOH (15 g, 455 mmol, 10 equiv) H_2O (50 ml) and MeOH (200 ml) was stirred at 50°C for 2h. The mixture was cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the MeOH was removed *in vacuo* and the residue was partitioned between saturated aqueous $NaHCO_3$ solution and AcOEt. The aqueous phase was re-extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-amino-5-ethoxy-benzoic acid methyl ester (D49) (8.8 g, 99%) as a pale green solid which was used in the next step without further purification. $[M+H]^+$ = 196.1, RT = 2.49 min

Description 50

3-Amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50)

3-Benzyloxy-5-(2-trimethylsilanyl-ethoxycarbonylamino)-benzoic acid methyl ester (D48) (8.5 g, 21.2 mmol, 1 equiv) in THF (40 ml) was treated with 1M tetrabutyl ammonium fluoride in

THF (40 ml, 40 mmol, 1.9 equiv) and the resulting solution stirred at room temperature for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and washed with H_2O (200 ml) then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was redissolved in Et_2O/EtOAc and treated with 2N HCl in Et_2O to give, after filtration, 3-amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50) (5.0 g, 80%) as a white solid.

Description 51

3-(4-Chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51)

3-Amino-5-ethoxy-benzoic acid methyl ester (D49) (4.0 g, 20.5 mmol, 1 equiv) was suspended in CH_2Cl_2 (40 ml) and treated at room temperature with NEt_3 (2.32 g, 23mmol, 1.1 equiv). The resulting solution was cooled to 0°C and 4-chlorobutyryl chloride (3.1 g, 22 mmol, 1.1 equiv) was added dropwise. The resulting mixture was stirred at 0°C for 3 h then allowed to warm to room temperature. The solution was washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give of 3-(4-chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51) (7.0 g, 115%) as a brown oil.

Description 52

3-Benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52)

A suspension of 3-amino-5-benzyloxy-benzoic acid methyl ester hydrochloride (D50) (5.0 g, 17 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with DMAP (400 mg, 3.2 mmol) and pyridine (3.5 g, 44 mmol, 2.6 equiv) followed by 3-chloropropanesulfonyl chloride (3.54 g, 20 mmol, 1.2 equiv) dropwise at room temperature. The resulting mixture was stirred for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52) (6.0 g, 97%) as a pale pink solid. $[M+H]^+$ = 366.1, RT = 2.34 min

Description 53

3-(3-Chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53)

A suspension of 3-amino-5-ethoxy-benzoic acid methyl ester (D49) (4.0 g, 20.5 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with DMAP (400 mg, 3.2 mmol,) and pyridine (1.74 g, 22 mmol, 1.1 equiv) followed by 3-chloropropanesulfonyl chloride (3.89 g, 22 mmol, 1.1 equiv) dropwise. The resulting mixture was stirred for 16 h then concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml), then dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(3-chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53) (6.7 g, 98%) as a pale orange solid.

Description 54

3-Benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54)

A solution of 3-benzyloxy-5-(3-chloro-propane-1-sulfonylamino)-benzoic acid methyl ester (D52) (6.0 g, 17 mmol, 1 equiv) in EtOH (80 ml) was treated with NEt_3 (3.4 g, 34 mmol, 2

equiv). The resulting mixture was refluxed for 6 h, cooled to room temperature and concentrated *in vacuo* to give 3-benzyloxy-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (D54) (4.5 g, 74%) as a pale pink solid.

Description 55

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55)

o a solution of 5-hydroxy-isophthalic acid dimethyl ester (D42) (21 g, 100 mmol, 1 equiv) in DMF (300 ml) at room temperature was added DABCO (14.6 g, 130 mmol, 1.3 equiv) followed by dimethylthiocarbamoyl chloride (14.8 g, 120 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 16 h and at 60°C for 2 h, then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the aqueous phase re-extracted with AcOEt. The combined organic solution was washed sequentially with 5% aqueous citric acid solution, 2N aqueous NaOH solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (23.5 g, 79%) as a pale yellow oil. $[M+H]^+$ = 298.0 ,RT = 3.06 min

Description 56

5-Dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56)

5-Dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (15.5 g, 52.2 mmol, 1 equiv) was stirred at 200°C for 24 h under nitrogen then cooled to room temperature. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 then 3/1) gave 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56) (7.0 g, 45%) and recovered 5-dimethylthiocarbamoyloxy-isophthalic acid dimethyl ester (D55) (2.77 g, 18%), both as white solids. $[M+H]^+$ = 298.0, RT = 2.92 min

Description 57

5-Dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57)

To a solution of 5-dimethylcarbamoylsulfanyl-isophthalic acid dimethyl ester (D56) (6 g, 20.2 mmol, 1 equiv) in THF (100 ml) at room temperature was added 2N aqueous NaOH solution (9.6 ml, 19.2 mmol, 0.95 equiv). The resulting mixture was stirred for 11 h and then partitioned between AcOEt and H_2O. The two layers were separated and the aqueous phase extracted with AcOEt. After acidification to pH 1, the aqueous phase was extracted twice with AcOEt. The organic solution was dried over $MgSO_4$ then concentrated *in vacuo* to give 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57) (4.54 g, 79%) as a white solid.

Description 58

***tert*-Butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58)**

To a solution of crude 5-dimethylcarbamoylsulfanyl-isophthalic acid monomethyl ester (D57) (4.56 g, 16.1 mmol, 1 equiv) in toluene (100 ml) was added triethylamine (6.7 ml, 48 mmol, 3 equiv) and diphenylphosphoryl azide (5.2 ml, 24 mmol, 1.5 equiv). The resulting mixture was stirred under nitrogen at 80°C for 3 h and then *tert*-butanol (4.6 ml, 48 mmol, 3 equiv) was added. The solution was stirred at 80°C for another 16 h then cooled to room temperature and

concentrated *in vacuo*. The crude product was dissolved in AcOEt and the resulting solution washed sequentially with 2N aqueous NaOH solution, 2N aqueous HCl solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 6/4) gave *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58) (2.24 g, 40%) as a white solid.

Description 59

3-*tert*-Butoxycarbonylamino-5-mercapto-benzoic acid (D59)

To a solution of *tert*-butoxycarbonylamino-dimethylcarbamoylsulfanyl-benzoic acid methyl ester (D58) (2.24 g, 6.3 mmol, 1 equiv) in MeOH (30 ml) and H_2O (23 ml) was added 2N aqueous NaOH solution (7 ml, 14mmol, 2.2 equiv). The resulting mixture was refluxed for 3 h and then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 1N aqueous NaOH solution. The aqueous phase was acidified to pH 1 and extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ then concentrated *in vacuo* to give 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (D59) (1.54 g, 90%) as a white solid.

Description 60

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60)

To a solution of 3-*tert*-butoxycarbonylamino-5-mercapto-benzoic acid (D59) (0.68 g, 2.52 mmol, 1 equiv) in acetone (15 ml) was added K_2CO_3 (3.5 g, 25.3 mmol, 10 equiv) and iodomethane (473 µl, 7.59 mmol, 3 equiv). The resulting mixture was stirred at 50°C for 2 h, cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 85/15) gave 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60) (0.47 g, 63%) as a white solid. $[M-H]^-$ = 296.1 ,RT = 3.51 min

Description 61

3-*tert*-Butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl ester (D61)

Description 61 was obtained from 0.68 g (2.53 mmol) of 3-*tert*-butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D59) and iodoethane using the procedure described in Description 60, which yielded the title compound (D61) (0.58 g, 71%) as a white solid. $[M-H]^-$ = 324.2, RT = 3.79 min

Description 62

3-Amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62)

3-*tert*-Butoxycarbonylamino-5-methylsulfanyl-benzoic acid methyl ester (D60) (0.54 g, 1.82 mmol, 1 equiv) was dissolved in dioxan (2 ml) and 4M HCl in dioxan (16 mmol, 4 ml, 8.8 equiv) was added. The solution was stirred at room temperature for 2 h allowing the hydrochloride salt of the amine to precipitate. This precipitate was filtered off, washed with Et_2O and dried giving 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (0.224 g, 52%). $[M+H]^+$ = 198.1, RT = 2.68 min

Description 63

3-Amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63)

Description 63 was prepared from 0.57 g (1.75 mmol) of 3-*tert*-butoxycarbonylamino-5-ethylsulfanyl-benzoic acid ethyl (D61) in an analogous manner to that described in Description 62 which yielded 0.335 g (73%) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) as a white solid. $[M+H]^+$ = 226.1, RT = 3.13 min

Description 64

3-(4-Chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64)

To a solution of 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (0.13 g, 0.556 mmol, 1 equiv) in dry CH_2Cl_2 (2 ml) at 0°C was added NEt_3 (193 ml, 1.39 mmol, 2.5 equiv) then 4-chlorobutyryl chloride (69 ml, 0.612 mmol, 1.1 equiv), dropwise, over 2 min. The resulting solution was stirred at 0°C for 15 min then at room temperature for 30 min. The solution was then diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64) (173 mg , 103%) as pale yellow crystals. $[M+H]^+$ = 302.0, RT = 3.20 min

Description 65

3-(4-Chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65)

Description 65 was prepared from 140 mg (0.535 mmol) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) in an analogous manner to that described in Description 64 which yielded 182 mg (103%) of 3-(4-chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65) as pale yellow crystals. $[M+H]^+$ = 330.0, RT = 3.51 min

Description 66

3-(3-Chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66)

To a solution of 3-amino-5-methylsulfanyl-benzoic acid methyl ester hydrochloride (D62) (130 mg, 0.556 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was added pyridine (142 ml, 1.75 mmol, 3 equiv), DMAP (6.8 mg, 0.056 mmol, 0.1 equiv) and then 3-chloropropane sulfonyl chloride (71 µl, 0.584 mmol, 1.05 equiv) dropwise over 2 min. The resulting mixture was stirred at room temperature for 2 h, diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(3-chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66) (196 mg, 104%) as light brown crystals.

$[M-H]^-$ = 336.0 RT = 3.20 min

Description 67

3-(3-Chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67)

Description 67 was prepared from 140 mg (0.6 mmol) of 3-amino-5-ethylsulfanyl-benzoic acid ethyl ester hydrochloride (D63) in an analogous manner to that described in Description 66

which yielded 200 mg (102%) of crude 3-(3-chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67) as light brown crystals.
$[M-H]^-$ = 364.0, RT = 3.49 min

Description 68

3-(2-Oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68)

To a solution of 3-bromo-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (D10) (500 mg, 1.4 mmol, 1 equiv) in DME (14 ml) and H_2O (4 ml) was added tetrakis(triphenylphosphine)-palladium(0) (81 mg, 0.07 mmol, 0.05 equiv), and the suspension was stirred for 10 min. 2,4,6 Tripropenylcyclotriboroxane-pyridine complex (394 mg, 1.4 mmol, 1 equiv) and K_2CO_3 (193 mg, 1.4 mmol, 1 equiv) were added and the resulting mixture was stirred at 90°C for 1 h, cooled to room temperature and diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (iso-hexane/AcOEt : 4/1) gave 3-(2-oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68) (480 mg, 100%) of adduct as a pale yellow oil. $[M+H]^+$ = 316.2, RT = 3.41 min

Descriptions 69-72

Descriptions 69-72 were prepared in an analogous manner to that described for Description 68 from the appropriate aryl bromide starting material indicated in the below table using the appropriate 2,4,6 trialkenylcyclotriboroxane-pyridine complex as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, **2002**, *67*, 4968-4971:

Description	Aryl bromide	$[M+H]^+$	RT (min)
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D69)	D18	(-*t*Bu) 296.1	3.61
3-(2-Oxo-pyrrolidin-1-yl)-5-vinyl-benzoic acid methyl ester (D70)	D9a		
3-Isopropenyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D71)	D9a	260.0	2.96
3-(2-Oxo-pyrrolidin-1-yl)-5-(E/Z)-propenyl-benzoic acid methyl ester (D72)	D9a	260.0	2.97

Description 73

3-Cyclopent-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester;
3-Cyclopent-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester; and
3-Cyclopent-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D73)

To a solution of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (686 mg, 2.3 mmol, 1 equiv) in DMF (3 ml) was added cyclopentene (409 µl, 4.6 mmol, 2 equiv), palladium(II)acetate (26 mg, 0.12 mmol, 0.05 equiv), tri(*o*-tolyl)phosphine (71 mg, 0.23 mmol, 0.1 equiv) and triethylamine (969 µl, 7 mmol, 3 equiv). The resulting mixture was stirred at 125°C for 16 h then cooled to room temperature and partitioned between H_2O and Et_2O. The two layers were separated and the organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give a mixture of 3-cyclopent-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl

ester, 3-cyclopent-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester and 3-cyclopent-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D73) (562 mg, 85%) as a brown oil.

Description 74

3-Cyclohex-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester;
3-Cyclohex-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester; and
3-Cyclohex-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D74)

Description 74 was prepared in an analogous manner to that described for Description 73 from 686 mg (mmol) of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) and cyclohexene which yielded 207 mg (30%) of 3-cyclohex-2-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester, 3-cyclohex-3-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester and 3-cyclohex-1-enyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D74) after purification by flash chromatography on silica gel (iso-hexane/EtOAc : 5/1)

Description 75

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75)

To a solution of 3-bromo-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid *tert*-butyl ester (D17) (376 mg, 1 mmol, 1 equiv) in DME (5 ml) and H_2O (5 ml) were added K_2CO_3 (345 mg, 2.5 mmol, 2.5 equiv), CuI (8 mg, 0.04 mmol, 0.04 equiv), triphenyl phosphine (21 mg, 0.08 mmol, 0.08 equiv), 10% palladium on charcoal (21 mg, 0.02 mmol, 0.02 equiv) and the solution was stirred at room temperature for 15 min. 2-Methyl-3-butyne-2-ol (254 µl, 2.5 mmol, 2.5 equiv) was added and the resulting mixture was stirred at 80°C for 16 h then cooled to room temperature. The catalyst was removed by filtration through a pad of celite and the filtrate was diluted with AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (iso-hexane/AcOEt : 4/1 to 2/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75) (142 mg, 37%) as a colorless oil which solidified on standing.

Description 76

3-(3-Hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76)

Description 76 was prepared using an analogous process to that described for Description 75 from 390 mg of 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D9b) which yielded 300 mg (76%) of 3-(3-hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76) as a white foam.

Description 77

5-nitro-isophthalic acid monomethyl ester (D77)

Description 77 is commercially available from Sigma-Aldrich Company.

Description 78

5-Nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78)

A mixture of 5-nitro-isophthalic acid monomethyl ester (D77) (5.0 g, 22.2 mmol, 1 equiv), *tert*-BuOH (8.2 g, 111 mmol, 5 equiv), EDAC.HCl (4.8 g, 25 mmol, 1.1 equiv) and DMAP (205 mg, 1.68 mmol, 0.07 equiv) dissolved in CH_2Cl_2 (50 ml) was stirred for 1 h at room temperature The mixture was then diluted with CH_2Cl_2 (50 ml), washed with 2N aqueous HCl solution (50 ml) and saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give of 5-nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78) (5.3 g, 85%) as a pale yellow oil.

Description 79

5-Amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79)

A mixture of 5-nitro-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D78) (5.3 g, 19 mmol, 1 equiv), NH_4COOH (11.9 g, 190 mmol, 10 equiv) and 10% Palladium on charcoal (50% wet, 0.75g, 7%w/w) in EtOH (50 ml) and H_2O (25 ml) was heated at 50 °C for 30 min. MeOH (20 ml) was added and the resulting solution was heated at 50 °C for another hour then cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The residue was diluted with saturated aqueous $NaHCO_3$ solution (100 ml) and the aqueous phase was extracted with AcOEt (150 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (3.4 g, 71%) as a white solid.

Description 80

5-(4-Chloro-butanoylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D80)

A suspension of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (3.4 g, 13.5 mmol, 1 equiv) in CH_2Cl_2 (25 ml) was treated with NEt_3 (2.32 g, 23 mmol, 1.1 equiv) and cooled to 0°C. 4-chlorobutyryl chloride (1.6 g, 15.7 mmol, 1.1 equiv) was added dropwise and the resulting solution was stirred at 0 °C for 3 h then allowed to warm to room temperature and washed with 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane and Et_2O to give 5-(4-chloro-butanoylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D80) (4.5 g, 94%) as a white solid.

Description 81

5-(3-Chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81)

To a solution of 5-amino-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D79) (5.0 g, 20 mmol, 1 equiv), DMAP (0.3 g, 2.46 mmol, 0.12 equiv) and pyridine (1.64 g, 20 mmol, 1 equiv) in CH_2Cl_2 (80 ml) was added 3-chloropropanesulfonyl chloride (2.4 ml, 20 mmol, 1 equiv) dropwise. The resulting mixture was stirred for 16 h then diluted with AcOEt (150 ml). The organic phase was washed with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(3-chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81) (7.8 g, 99%) as a pale orange solid.

Description 82

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82)

A mixture of 5-(3-chloro-propane-1-sulfonylamino)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D81) (7.8 g, 20 mmol, 1 equiv) and NEt_3 (4.0 g, 40 mmol, 2 equiv) in EtOH (100 ml) was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82) (4.4 g, 62%) as a white solid.

Description 83

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (D82) (4.4 g, 12.4 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was treated with TFA (10ml) and the resulting mixture was stirred for 2 h at room temperature. Toluene (10 ml) was added and the resulting mixture was concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (3.6 g, 97%)as a white solid.

Description 84

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84)

A solution of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (500 mg, 1.67 mmol, 1 equiv) in THF (30 ml) was treated with BH_3-Me_2S (2M solution in THF, 1.0 ml, 2 mmol, 1.2 equiv) and the mixture was refluxed for 30 min and then cooled to room temperature. MeOH (5 ml) was added dropwise and the resulting mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (100 ml), and the resulting solution was washed with 2N aqueous HCl solution (100 ml) and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$. and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (450 mg, 95%) as a clear, colourless oil.

Description 85

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (D84) (400 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (20 ml) was treated with NEt_3 (303 mg, 3.0 mmol, 2.1 equiv) and methanesulfonic anhydride (261 mg, 1.5 mmol, 1.1 equiv) and stirred for 30 min at room temperature. The solution was then washed with 2N aqueous HCl solution (30 ml) and saturated aqueous $NaHCO_3$ solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated in Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (390 mg, 77%) as a white solid.

Description 86

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (500 mg, 1.8 mmol, 1 equiv) in CH_2Cl_2 (20 ml) was treated with MnO_2 (763 mg, 8.8 mmol, 4.9 equiv) and the resulting mixture was stirred for 3 h at room temperature. A second portion of MnO_2 (500 mg, 5.8 mmol, 3.2 equiv) was added and the mixture stirred for 3 h when a third portion of MnO_2 (300mg, 3.5 mmol, 1.9 equiv) was added. The mixture was stirred for 2 h and then filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) (450 mg, 88%) as a yellow waxy solid.

Description 87

5-Nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87)

A suspension of 5-nitro-isophthalic acid monomethyl ester (D77) (1.0 g, 4.44 mmol, 1 equiv) in CH_2Cl_2 (40 ml) was treated with $(COCl)_2$ (655 mg, 5.2 mmol, 1.2 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 1 h at room temperature and then dipropylamine (1.65 g, 15 mmol, 3.4 equiv) was added and the resulting solution stirred for a further 30 min. The solution was then washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml) , dried over $MgSO_4$ and concentrated *in vacuo* to give 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87) (1.5 g, 110%) as a pale yellow oil.

Description 88

5-Amino- *N,N*-dipropyl-isophthalamic acid methyl ester (D88)

A mixture of 5-nitro-*N,N*-dipropyl-isophthalamic acid methyl ester (D87) (1.5 g, 4.9 mmol, 1 equiv), NH_4COOH (3.0 g, 49 mmol, 10 equiv), 10% Pd on charcoal (50% wet, 250 mg, 0.082 equiv w/w), EtOH (20 ml) and H_2O (10 ml) was heated at 50°C for 90 min. The mixture was cooled to room temperature, filtered through a pad of celite and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with saturated $NaHCO_3$ solution (100ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.2 g, 88%) as a white waxy solid.

Description 89

5-(4-Chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89)

A solution of 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.2 g, 4.3 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was treated with NEt_3 (525 mg, 5.2 mmol, 1.2 equiv). The solution was cooled to 0 °C and 4-chlorobutyryl chloride (733 mg, 5.0 mmol, 1.2 equiv) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 1 h. The solution was washed with 2N aqueous HCl solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(4-chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89) (1.7 g, 104%) as a colourless oil.

Description 90

5-(5-Chloro-pentanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D90)
Description 90 was prepared in an analogous manner to Description 89 from 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) and 5-chlorovaleryl chloride.

Description 91
5-(3-Chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91)
A solution of 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) (1.4 g, 5.0 mmol, 1 equiv), DMAP (100 mg) and pyridine (392 mg, 5.0 mmol, 1.1 equiv) in CH_2Cl_2 (20 ml) was treated dropwise with 3-chloropropane-1-sulfonyl chloride (946 mg, 5.3 mmol, 1.1 equiv). The resulting mixture was stirred for 16 h at room temperature and then diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (50 ml) followed by saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(3-chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91) (1.8 g, 86%) as a pink solid.

Description 92
5-(4-Chloro-butane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D92)
Description 92 was prepared in an analogous manner to Description 91 from 5-amino-*N,N*-dipropyl-isophthalamic acid methyl ester (D88) and 4-chloro-butane-1-sulfonyl chloride.

Description 93
(2S,3R)-3-Hydroxy-2-((S)-2-hydroxy-1-phenyl-ethylamino)-hexanoic acid methyl ester (D93)
Description 93 was obtained according to Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; David, J.; Williams, C. E. *Tetrahedron*, **54 (22)**, 1998, 6089-6098.

Description 94
(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94)
(2S,3R)-3-Hydroxy-2-((S)-2-hydroxy-1-phenyl-ethylamino)-hexanoic acid methyl ester (D93) (2.88 g, 10.25 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 2 g, 35% w/w), HCOOH (5 ml, excess) in MeOH (50 ml) were stirred at 60°C for 1 h. The mixture was then cooled to room temperature, filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in dioxan/water (1/1, 50 ml) and $NaHCO_3$ (10g, excess) then di-*tert*-butyl dicarbonate (3.37 g, 15 mmol, 1.5 equiv) were added. The resulting mixture was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed successively with 2N aqueous HCl solution and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1) gave (2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94) (1.88 g, 70%) as a colourless gum.

Description 95

(S)-2-*tert*-butoxycarbonylamino-4-methylsulfanyl-butyric acid (D95)

Description 95 is commercially available from Sigma-Aldrich Company.

Description 96

((S)-1-Isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96)

(S)-2-*tert*-butoxycarbonylamino-4-methylsulfanyl-butyric acid (D95) (2.0 g, 8.0 mmol, 1 equiv), EDAC.HCl (1.84 g, 9.6 mmol, 1.2 equiv), HOBT (1.47 g, 9.6 mmol, 1.2 equiv), 4-ethylmorpholine (1.76 g, 16 mmol, 2 equiv) and *iso*-butylamine (952 ml, 9.6 mmol, 1.2 equiv) in CH_2Cl_2 (10 ml) were stirred at room temperature for 16 h. The solution was concentrated *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give ((S)-1-isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96) (2.38 g, 98%) as a colourless oil.

Description 97

(3-methoxy-phenyl)-acetic acid ethyl ester (D97)

Description 97 is commercially available from Sigma-Aldrich Company.

Description 98

2-(3-Methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98)

To a solution of (3-methoxy-phenyl)-acetic acid ethyl ester (D97) (19.72 g, 0,101 m, 1 equiv) in THF (200 ml) was added NaH (8.8g, 0.222 mol, 2.2 equiv) then iodomethane (26 ml, 0.4 mol, 4 equiv). The resulting mixture was stirred at room temperature for 16 h then partitioned between AcOEt and a saturated $NaHCO_3$ aqueous solution. The two layers were separated and the organic phase washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98) (20.85 g, 98%) as an orange oil.

Description 99

2-(3-Methoxy-phenyl)-2-methyl-propionic acid (D99)

To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (D98) (20.95g, 94 mmol, 1 equiv) in EtOH (200 ml) was added 2N NaOH aqueous solution (90 ml, 180 mmol, 1.9 equiv) and the resulting mixture was stirred at 70°C for 16 h then cooled to room temperature. Most of EtOH was removed *in vacuo* and the residue extracted with AcOEt then acidified to pH 1. The aqueous phase was then extracted with AcOEt and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 2-(3-methoxy-phenyl)-2-methyl-propionic acid (D99) (15g, 82%) as a yellow oil.

Description 100

[1-(3-Methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100)

To a solution of 2-(3-methoxy-phenyl)-2-methyl-propionic acid (D99) (1g, 5.15 mmol, 1 equiv) in toluene (20 ml) at room temperature was added NEt_3 (1.07 ml, 7.72 mmol, 1.5 equiv) and

then diphenylphosphoryl azide (2.2 ml, 10.3 mmol, 2 equiv). The resulting mixture was then heated at 80°C for 2 h then benzyl alcohol (1.61 ml, 15.45 mmol, 3 equiv) was added and the solution heated for a further 2 h, cooled to room temperature and partitioned between EtOAc and a saturated $NaHCO_3$ aqueous solution. The two layers were separated and the aqueous phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1) gave [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100) (1g, 65%) a yellow gum.

Description 101

((S)-(S)-1-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101)

Description 101 is commercially available from Chirex (ref 1819W94, lot#9924382).

Description 102

((1S,2R)-3-Amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102)

To a solution of ((S)-(S)-1-oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101) (25 g, 95.1 mmol, 1 equiv)) in MeOH (350 ml) was added aqueous ammonia (32% w/w, 180 ml, 3.2 mol, 3.3 equiv). The resulting mixture was stirred at room temperature for 16 h then concentrated *in vacuo* to give ((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102) (25.2 g, 95%) as a white solid.

Description 103

((2R,3S)-3-*tert*-Butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103)

A solution of ((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (D102) (25.6 g, 91.4 mmol, 1 equiv) in DMF (250 ml) at 0°C was treated with NEt_3 (15 ml, 108 mmol, 1.2 equiv) and then with benzyl chloroformate (14 ml, 98 mmol, 1.1 equiv) in DMF (50 ml) dropwise. The resulting solution was stirred at 0°C for 1 h and at room temperature for 16 h and then concentrated *in vacuo*. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The resulting precipitate was diluted with H_2O and filtered to give ((2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103) (31.5 g, 83%) as a white solid.

Description 104

((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D104)

A solution of ((2R,3S)-3-*tert*-butoxycarbonylamino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D103) (31.5 g, 76.1 mmol, 1 equiv) in THF (300 ml) was treated with 4N HCl solution in dioxan (40 ml, 160 mmol, 2.1 equiv). The resulting solution was stirred at room temperature for 2 h then concentrated *in vacuo*. The residue was triturated with Et_2O/*iso*-hexane to give ((2R,3S)-3-amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester hydrochloride (D104) (22.1 g, 83%) as a white solid.

Description 105

[(2R,3S)-2-Hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105)

To a suspension of 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid (A13) (530 mg, 1.82 mmol, 1 equiv) in CH_2Cl_2 (20 ml) were added HOBT (300 mg, 2.2 mmol, 1.2 equiv) and EDAC.HCl (420 mg, 2.2 mmol, 1.2 equiv). After stirring for 5 min, 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid hydrochloride (D104) (570 mg, 1.82 mmol, 1 equiv) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 ml) washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give [(2R,3S)-2-hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105) (510 mg, 48 %) as a white solid.

Description 106

[(2R,3S)-3-({1-[3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D106)

Description 106 was prepared in an analogous manner to Description 105 from 3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid hydrochloride (D104) and 3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A31).

Description 107

[(2R,3S)-3-({1-[3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D107)

Description 107 was prepared in an analogous manner to Description 105 from 3-(2-oxo-pyrrolidin-1-yl)-5-isopropylamino-benzoic acid hydrochloride (A44) and ((2R,3S)-3-amino-2-hydroxy-4-phenyl-butyl)-carbamic acid benzyl ester (D104).

Description 108-119

The following compounds (D108-D119) were prepared from Description 104 in an analogous manner to the process described for Description 105 using the appropriate acid.

Description	Acid
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D108)	A73
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorophenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D109)	A119
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D110)	A107
Phenylmethyl [(2*R*,3*S*)-2-hydroxy-3-({[3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-4-phenylbutyl]carbamate (D111)	A12
Phenylmethyl {(2*R*,3*S*)-3-[({3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-2-hydroxy-4-phenylbutyl}carbamate (D112)	A168
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-	A126

2-yl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D113)	
Phenylmethyl [(2*R*,3*S*)-3-({[3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D114)	A11
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D115)	A18
Phenylmethyl {(2*R*,3*S*)-3-[({3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl) oxy]phenyl}carbonyl)amino]-2-hydroxy-4-phenylbutyl}carbamate (D116)	A19
Phenylmethyl [(2*R*,3*S*)-3-({[3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl) phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D117)	A169
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D118)	A70
Phenylmethyl [(2*R*,3*S*)-3-({[3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)phenyl]carbonyl}amino)-2-hydroxy-4-phenylbutyl]carbamate (D119)	A170

Description 120-131

The following compounds (D120-D131) were prepared in an analogous manner to the process described for Example 182 using the appropriate precursor:

Description	Precursor
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzamide (D120)	D108
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido tetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (D121)	D109
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide (D122)	D110
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (D123)	D111
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide (D124)	D112
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzamide (D125)	D113
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide (D126)	D114
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide (D127)	D115
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide (D128)	D116
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide (D129)	D117
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide (D130)	D118
N-[(1*S*,2*R*)-3-Amino-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide (D131)	D119

Description 132

Methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132)

Methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132) was prepared from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to that described for Description 68 (D68). No molecular ion. RT = 3.42 min.

Description 133

Methyl 3-amino-5-propylbenzoate (D133)

Methyl 3-amino-5-propylbenzoate (D133) was prepared from methyl 3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D132) in an analogous manner to that described for Ester 116 (B116).

Description 134

Methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134)

To a solution of methyl 3-amino-5-propylbenzoate (D133) (2.49 g, 12.9 mmol, 1 equiv) in CH_2Cl_2 (25 ml) were added pyridine (1.13 ml, 14 mmol, 1.1 equiv), 2-propene-1-sulfonyl chloride (2 g, 12.9 mmol, 1 equiv) and DMAP (350 mg, 2.9 mmol, 0.2 equiv) and the resulting mixture was stirred at room temperature for 4 days. The solution was diluted with AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 4:1) gave methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134) (1.3 g, 32%) as a colourless oil. $[M-H]^-$ = 310.0, RT = 3.39 min.

Description 135

Methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135)

To a solution of methyl 3-[(3-buten-1-ylsulfonyl)amino]-5-propylbenzoate (D134) (1.3 g, 4.2 mmol, 1 equiv), 2-propen-1-ol (280 µl, 4.2 mmol, 1 equiv) and triphenylphosphine (1.28 g, 4.9 mmol, 1.15 equiv) in toluene (20 ml) at room temperature was slowly added diisopropyl azodicarboxylate (964 ml, 4.9 mmol, 1.15 equiv). The resulting solution was stirred at this temperature for 30 min then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 4:1) gave methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135) (1.1 g, 75%) as a yellow oil.
$[M+H]^+$ = 352.1, RT = 3.63 min.

Description 136

2-Fluoro-3,5-dinitrobenzoic acid (D136)

A 70% aqueous HNO_3 solution (80 ml) was added dropwise to H_2SO_4 (160 ml). The temperature was kept below 10°C using an ice-bath. 2-Fluoro benzoic acid (14 g, 0.1 mol, 1 equiv) was added portionwise over 5 min then the colorless suspension was slowly warmed to 90°C and stirred at this temperature for 1 h then at 100°C for 3 h. The solution was then cooled to room temperature and carefully poured into ice (1 l) diluted with H_2O (1.5 l). The aqueous phase was extracted 3 times with AcOEt and the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 2-fluoro-3,5-

dinitrobenzoic acid (D136) (13.6 g, 59%) as a pale yellow solid which was used in the next step without further purification. No molecular ion, RT = 2.06 min.

Description 137

Methyl 2-fluoro-3,5-dinitrobenzoate (D137)

Methyl 2-fluoro-3,5-dinitrobenzoate (D137) was prepared in an analogous manner to Description 25 (D25) from 2-fluoro-3,5-dinitrobenzoic acid (D136).

Description 138

Methyl 3-amino-2-fluoro-5-nitrobenzoate (D138)

To a solution of methyl 2-fluoro-3,5-dinitrobenzoate (D137) (24.4 g, 0.1 mol, 1 equiv) in AcOH (1 l) was added iron (27.5 g, 0.5 mol, 5 equiv) and the resulting suspension was vigorously stirred for 1 h. The temperature was kept below 35°C by small amount of cooling using an ice bath during that period. Toluene (200 ml) was added and the suspension filtered through a pad of celite. The remaining solution was concentrated *in vacuo* and the residue partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (17 g, 79%) as a yellow solid which was used in the next step without further purification. $[M-H]^-$ = 212.9, RT = 2.68 min.

Description 139

Methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139)

To a solution of methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (12 g, 56 mmol, 1 equiv) in CH_2Cl_2 (150 ml) at room temperature were added NEt_3 (11.7 ml, 84 mmol, 1.5 equiv) and 4-chlorobutanoyl chloride (6.9 ml, 61.6 mmol, 1.1 equiv) and the resulting mixture was stirred for 2 h then washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 4/1) gave methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139) (16.2 g, 91%) as a yellow solid. $[M+H]^+$ = 319.1, RT = 3.12 min.

Description 140

Methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140)

To a solution of methyl 3-[(4-chlorobutanoyl)amino]-2-fluoro-5-nitrobenzoate (D139) (8.5 g, 26.7 mmol, 1 equiv) in THF (100 ml) was added NaH (60% dispersion in mineral oil, 1.17 g, 29.4 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 1.5 h then diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1) gave methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140) (3.3 g, 43%) as a yellow solid. $[M+H]^+$ = 283.1, RT = 2.53 min.

Description 141

Methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141)
To a solution of methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) (500 mg, 2.34 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (840 µl, 6.0 mmol, 2.6 equiv) then 3-chloro-1-propanesulfonyl chloride (624 µl, 5.0 mmol, 2.1 equiv) and the resulting mixture was stirred for 1 h. The organic phase was then washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) (900 mg, 78%) as a brown foam which was used in the next step without further purification. No molecular ion, RT = 3.51 min.

Description 142
Methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142)
Methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142) was obtained from methyl 3-amino-2-fluoro-5-nitrobenzoate (D138) in an analogous manner to that described for methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) using 4-chloro-1-butanesulfonyl chloride (D20) instead of 3-chloro-1-propanesulfonyl chloride. $[M+H+NH_3]+$ = 540.1, RT = 3.62 min.

Description 143
3-{[(3-Chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143)
To a solution of crude methyl 3-{bis[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D141) (900 mg, 1.81 mmol, 1 equiv) in MeOH (25 ml) was added a 2N aqueous NaOH solution (15 ml, 30 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O/*iso*-hexane to give 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143) (600 mg, 97%) as a light tan solid which was used in the next step without further purification. No molecular ion, RT = 3.05 min.

Description 144
3-{[(4-Chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D144)
3-{[(4-Chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D144) was obtained from methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D142) in an analogous manner to the process described for 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143).

Description 145
Methyl 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D145)
Methyl 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D145) was prepared in an analogous manner to Description 25 from 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D143). $[M-H]^-$ = 353.0, RT = 3.05 min.

Description 146

Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D146)

Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D146) was prepared in an analogous manner to Description 25 from 3-{[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoic acid (D144). $[M+H+NH_3]^+$ = 386.1, RT = 3.13 min.

Description 147

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147)

To a solution of methyl 3-{[(3-chloropropyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D145) (300 mg, 0.85 mmol, 1 equiv) in EtOH (30 ml) was added NEt_3 (280 µl, 2 mmol, 2.3 equiv) and the resulting solution was refluxed for 1.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/Et_2O to give methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147) (150 mg, 55%) as a light tan solid which was used in the next step without further purification. $[M+H+ NH_3]+$ = 336.3, RT = 2.50 min.

Description 148

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-nitrobenzoate (D148)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-nitrobenzoate (D148) was prepared in an analogous manner to the process for methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-nitrobenzoate (D147) from methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D146). $[M+H+ NH_3]+$ = 350.1,RT = 2.79 min.

Description 149

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)-5-nitrobenzoate (D149)

To a solution of methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-2-fluoro-5-nitrobenzoate (D146) (1.5 g, 4.1 mmol, 1 equiv) in MeOH (30 ml) was added NEt_3 (1.2 ml 8.6 mmol, 2.1 equiv) and the resulting solution was refluxed for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/Et_2O to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)-5-nitrobenzoate (D149) (1.2 g, 55%) as a light brown solid which was used in the next step without further purification. $[M+H]+$ = 345.1, RT = 2.80 min.

Description 150

Methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150)

To a solution of methyl 2-fluoro-5-nitro-3-(2-oxo-1-pyrrolidinyl)benzoate (D140) (3.3 g, 11.7 mmol, 1 equiv) in EtOH (100 ml) and H_2O (10 ml) were added NH_4COOH (7.4 g, 117 mmol, 10 equiv) and 10% palladium on charcoal (50% wet, 660 mg, 10% w/w) and the resulting mixture was refluxed for 2 h then cooled to room temperature. The catalyst was removed by

filtration through a pad of celite and most of the solvent removed *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) (1.85 g, 63%) as a pale yellow solid which was used in the next step without further purification. $[M+H]^+$ = 253.0, RT = 2.12 min.

Descriptions 151-153 (D151-153)

The following compounds have been made from the appropriate precursor in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150).

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 5-amino-3-(1,1-dioxido-2-isothiazolidinyl)-2-fluorobenzoate (D151)	D147	289.1	2.12
Methyl 5-amino-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D152)	D148	303.1	2.33
Methyl 5-amino-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-(methyloxy)benzoate (D153)	D149	315.1	2.18

Description 154

Methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154)

Methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154) was prepared from methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) in an analogous manner to the process described for Ester 35 (B35) using 4-(methyloxy)benzaldehyde instead of propionaldehyde. $[M+H]^+$ = 373.4, RT = 2.85 min.

Description 155

Methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155)

Methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155) was prepared from methyl 2-fluoro-5-({[4-(methyloxy)phenyl]methyl}amino)-3-(2-oxo-1-pyrrolidinyl)benzoate (D154) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 401.4, RT = 3.11 min.

Description 156

Methyl 5-bromo-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D156)

To a solution of methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150) (650 mg, 2.6 mmol, 1 equiv) in a 48% aqueous HBr solution at 0°C was added $NaNO_2$ portionwise and the resulting mixture was stirred at 0°C for 30 min. CuBr (260 mg, 1.82 mmol, 0.7 equiv) in a 48% aqueous HBr solution (1 ml) was added and the resulting mixture stirred at 90°C for 1 h then cooled to room temperature and partitioned between H_2O and AcOEt. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1)

gave methyl 5-bromo-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D156) (145 mg, 18%) as a white solid. $[M+H]^+$ = 318.1, RT = 2.51 min.

Descriptions 157-158 (D157-158)

The following compounds were prepared in an analogous manner to the process described for Description 156 (D156) from the appropriate aniline:

Description	Precursor	RT (min)
Methyl 5-bromo-3-(1,1-dioxido-2-isothiazolidinyl)-2-fluorobenzoate (D157)	D151	2.55
Methyl 5-bromo-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D158)	D152	

Descriptions 159-161 (D159-161)

The following compounds were prepared in an analogous manner to the process described for Description 68 (D68) from the appropriate aryl bromide indicated in the below table:

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D159)	D156	278.4	2.60
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D160)	D157	314.2	2.67
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D161)	D158		

Description 162

Methyl 4-methyl-3,5-dinitrobenzoate (D162)

Methyl 4-methyl-3,5-dinitrobenzoate (D162) was prepared in an analogous manner to Description 25 from commercially available 4-methyl-3,5-dinitrobenzoic acid. $[M+H]^+$ = 240.2, RT = 3.07 min.

Description 163

Methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163)

To a solution of methyl 4-(methyloxy)-3,5-dinitrobenzoate (D25) (5.0 g, 19.5 mmol, 1 equiv) in AcOH (150 ml) at room temperature was added iron powder (9.0 g, 161 mmol, 8.2 equiv) portionwise and the resulting mixture was stirred for 3 h. Toluene (500 ml) was added and the organic phase was filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration of the residue with Et_2O/*iso*-hexane gave methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163) (3.65 g, 83%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 226.9, RT = 2.76 min.

Description 164

Methyl 3-amino-4-methyl-5-nitrobenzoate (D164)

Methyl 3-amino-4-methyl-5-nitrobenzoate (D164) was obtained from methyl 4-methyl-3,5-dinitrobenzoate (D162) in an analogous manner to the process described for methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163). $[M+H]^+$ = 211.0, RT = 2.81 min.

Description 165

Methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165)

To a solution of methyl 3-amino-4-(methyloxy)-5-nitrobenzoate (D163) (370 mg, 1.64 mmol, 1 equiv) in toluene (20 ml) at 0°C was added iodine (218 mg, 0.86 mmol, 0.5 equiv) then 1,1-dimethylethyl nitrite (200 mg, 1.75 mmol, 1.1 equiv) and the resulting mixture was stirred at room temperature for 15 h then partitioned between AcOEt and brine. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel gave methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165) (280 mg, 51%) as a light brown solid. No molecular ion. RT = 3.33 min.

Description 166

Methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166)

Methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166) was prepared from methyl 3-iodo-4-(methyloxy)-5-nitrobenzoate (D165) in an analogous manner to the process described for Description 68 (D68). No molecular ion. RT = 3.46 min.

Description 167

Methyl 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167)

To a solution of methyl 4-(methyloxy)-3-nitro-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D166) (1.0 g, 4.0 mmol, 1 equiv) in AcOH (150 ml) at room temperature was added iron powder (1.4 g, 25 mmol, 6.25 equiv) portionwise and the resulting mixture was stirred for 3 h at room temperature. Iron powder (1 g, 17.9 mmol, 4.2 equiv) was added and the mixture stirred for another hour. Iron powder (1 g, 17.9 mmol, 4.2 equiv) was then added again and the mixture stirred at 45°C for 3 h then cooled to room temperature and stirred at this temperature for 14 h. Toluene (200 ml) was added and the organic phase was filtered through a pad of celite then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167) (800 mg, 90%) as a brown oil which was used in the next step without further purification. $[M+H]^+$ = 222.1, RT = 2.99 min.

Description 168

Methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168)

To a solution of 3-amino-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D167) (800 mg, 3.6 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (1.5 ml, 10.8 mmol, 3.0 equiv) then 4-chloro-1-butanesulfonyl chloride (D20) (2 g, 10.8 mmol, 3.0 equiv) and the resulting mixture was stirred for 1 h. The organic phase was then washed with a 2N aqueous HCl solution and

a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 3/1) gave methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168) (1.0 g, 52%) as a pale yellow oil.

Description 169

3-{[(4-Chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169)

To a solution of methyl 3-{bis[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D168) (1.0 g, 1.88 mmol, 1 equiv) in MeOH (20 ml) was added a 2N aqueous NaOH solution (10 ml, 20 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O/*iso*-hexane to give 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169) (470 mg, 69%) as a light cream solid which was used in the next step without further purification. $[M-H]^-$ = 360.0, RT = 3.19 min.

Description 170

Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E*)-1-propen-1-yl]benzoate (D170)

Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D170) was prepared from 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (D169) in an analogous manner to Description 25 (D25).

Descriptions 171-172 (D171-172)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 3-[(4-chlorobutanoyl)amino]-4-(methyloxy)-5-nitrobenzoate (D171)	D163	331.0	3.13
Methyl 3-[(4-chlorobutanoyl)amino]-4-methyl-5-nitrobenzoate (D172)	D164	315.1	3.02

Descriptions 173-174 (D173-174)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 14 (D14):

Description	Precursor	$[M-H]^-$	RT (min)
Methyl 3-{[(3-chloropropyl)sulfonyl]amino}-4-(methyloxy)-5-nitrobenzoate (D173)	D163	364.9	3.10
Methyl 3-{[(3-chloropropyl)sulfonyl]amino}-4-methyl-5-nitrobenzoate (D174)	D164	349.0	3.12

Descriptions 175-176 (D175-176)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 14 (D14) using 4-chloro-1-butanesulfonyl chloride (D20) instead of 3-chloro-1-propanesulfonyl chloride:

Description	Precursor	$[M-H]^-$	RT (min)
Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-nitrobenzoate (D175)	D163		
Methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-4-methyl-5-nitrobenzoate (D176)	D164	362.8	3.21

Descriptions 177-178 (D177-178)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Ester 27 (B27):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 4-(methyloxy)-3-nitro-5-(2-oxo-1-pyrrolidinyl) benzoate (D177)	D171	295.1	2.61
Methyl 4-methyl-3-nitro-5-(2-oxo-1-pyrrolidinyl) benzoate (D178)	D172	279.0	2.60

Descriptions 179-182 (D179-182)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 15 (D15):

Description	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-4-(methyloxy)-5-nitrobenzoate (D179)	D173	331.0	2.78
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-4-methyl-5-nitrobenzoate (D180)	D174		
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-nitrobenzoate (D181)	D175	345.0	2.90
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methyl-5-nitrobenzoate (D182)	D176	329.0	2.93

Descriptions 183-188 (D183-188)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for the synthesis of Description 16 (D16) using the appropriate precursor indicated in the below table:

Description	Precursor	$[M+H]^+$	RT (min)
methyl 3-amino-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl) benzoate (D183)	D177	265.1	2.18
methyl 3-amino-4-methyl-5-(2-oxo-1-pyrrolidinyl) benzoate (D184)	D178	249.1	2.16
methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)-4-(methyloxy) benzoate (D185)	D179	301.0	2.25

methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)-4-methylbenzoate (D186)	D180	285.0	2.22
methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy) benzoate (D187)	D181	315.1	2.40
methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (D188)	D182	299.0	2.42

Description 189

4-((Z/E)-But-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189)

To a solution of 4-amino-3,5-diiodo-benzoic acid ethyl ester (commercially available from Maybridge) (72.6 g, 0.17 mmol, 1 equiv) in DMF (450 ml) at 0°C under nitrogen was added NaH (60% in mineral oil, 7.3 g, 0.18 mmol, 1.05 equiv) portionwise over 2 min. After 10 min crotyl bromide (21.5 ml, 0.21 mmol, 1.2 equiv) in DMF (50 ml) was added *via cannula* over 5 min and the resulting mixture was allowed to warm to room temperature over 30 min. 5 Ml of EtOH were added and the mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O. The aqueous phase was extracted with AcOEt and the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189) (82 g, 100%) as a pink solid which was used in the next step without further purification. $[M+H]^+$ = 472.0, RT = 4.93 min.

Description 190

3-Ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D190)

To a solution of 4-((Z/E)-but-2-enylamino)-3,5-diiodo-benzoic acid ethyl ester (D189) (15 g, 31.8 mmol, 1 equiv) in DMF (150 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (357 mg, 1.6 mmol, 0.05 equiv), NaCOOH (6.5 g, 95.6 mmol, 3 equiv), Na_2CO_3 (8.4 g, 79.6 mmol, 2.5 equiv) and NBu_4Cl (8.0 g, 35.0 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 80°C for 30 min then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 9/1) gave 3-ethyl-7-iodo-1 *H*-indole-5-carboxylic acid ethyl ester (D190) (6.3 g, 58%) as a white solid. $[M+H]^+$ = 344.0, RT = 3.86 min.

Description 191

1,1-Dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191)

A flask was charged under nitrogen with 3-bromo-5-iodo-benzoic acid methyl ester (D8b) (840 mg, 2.2 mmol, 1.1 equiv) , Cs_2CO_3 (900 mg, 2.8 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (92 mg, 0.1 mmol, 0.05 equiv), Xantphos (120 mg, 0.2 mmol, 0.1 equiv) and toluene (40 ml). 5-Phenyl-2-piperidinone (Koelsch, *J. Am. Chem. Soc.* **1943**, (65), 2093, 350 mg, 2 mmol, 1equiv) was then added and the resulting mixture was stirred at 100°C for 2.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The

layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a solid residue. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 4/1 to 1/1) gave 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191) (480 mg, 51%) as a white solid. $[M+H]^+$ = 432.2, RT = 3.82 min.

Description 192

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192)

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192) was prepared in an analogous manner to the process described for Description 68 (D68) from 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D191). $[M+H]^+$ = 392.3, RT = 3.83 min.

Description 193

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193) was obtained from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to the process described for Description 15 (D15) (alternative procedure) using tetrahydro-2*H*-1,2-thiazine 1,1-dioxide (D22b) instead of isothiazolidine 1,1-dioxide (D22a). $[M+H+NH_3]^+$ = 332.2, RT = 2.75 min.

Description 194

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194)

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D193) in an analogous manner to the process described for Description 2 (D2).
$[M+H]^+$ = 285.1, RT = 2.12 min.

Description 195

Methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195)

Methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195) was obtained from methyl 3-amino-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D16) in an analogous manner to the process described for Description 13 (D13).

Description 196

Methyl 3-amino-4-methyl-5-nitrobenzoate (D196)

To a solution of methyl 4-methyl-3,5-dinitrobenzoate (D162) (30 g, 0.125 mmol, 1 equiv) in MeOH (150 ml) and cyclohexene (300 ml) was added 10% palladium on charcoal (50% wet, 3 g, 5% w/w) and the resulting suspension was refluxed for 7 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the solvent was removed *in vacuo*. The precipitate formed was filtered off to give methyl 3-amino-4-methyl-5-nitrobenzoate (D196) (22 g, 84%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 211.0, RT = 2.81 min.

Description 197

Methyl 4-nitro-1*H*-indazole-6-carboxylate (D197)

To a suspension of 3-amino-4-methyl-5-nitrobenzoate (D196) (3.5 g, 16.7 mmol, 1 equiv) in H_2O (100 ml) at 0°C was added 36% aqueous HCl solution (15 ml) and the resulting suspension was treated with $NaNO_2$ (1.35 g, 19.6 mmol, 1.2 equiv) then warmed to room temperature and stirred for 1.5 h. The insoluble material was removed by filtration and small amounts of urea were added to the mother liquors. The resulting solution was diluted with H_2O (500 ml) and treated with H_2SO_4 (17.5 ml) then heated at 50°C for 15 min, cooled to room temperature and extracted with AcOEt. The organic phase was dried over $MgSO_4$ then concentrated *in vacuo*. The residue was triturated with MeOH to give methyl 4-nitro-1*H*-indazole-6-carboxylate (D197) (0.8 g, 22%) as a cream solid which was used in the next step without further purification. $[M+H]^+$ = 222.1, RT = 2.84 min.

Description 198

Methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198)

To a solution of methyl 4-nitro-1*H*-indazole-6-carboxylate (D197) (500 mg, 2.3 mmol, 1 equiv) in DMF (10 ml) at room temperature was added K_2CO_3 (346 mg, 2.5 mmol, 1.1 equiv) then ethyl iodide (200 µl, 2.5 mmol, 1.1 equiv). The resulting suspension was stirred at room temperature for 15 min then at 40°C for 30 min, cooled to room temperature and partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 2/1) gave methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198) (200 mg, 35%) as a pale yellow solid. $[M+H]^+$ = 250.1, RT = 3.11 min.

Description 199

Methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate (D199)

To a solution of methyl 1-ethyl-4-nitro-1*H*-indazole-6-carboxylate (D198) (2.2 g, 8.8 mmol, 1 equiv) in MeOH (100 ml) and H_2O (10 ml) was added 10% palladium on charcoal (50% wet, 700 mg, 16% w/w) and the resulting mixture was stirred at 60°C for 30 min then cooled to room temperature. The catalyst was removed by filtration through a pad of celite and most of the solvent removed *in vacuo*. The residue was partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution and the two layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate (D199) (1.55 g, 80%) which was used in the next step without further purification. $[M+H]^+$ = 220.1, RT = 3.31 min.

Description 200

Methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200)

To a solution of methyl 4-methyl-3,5-dinitrobenzoate (D162) (20 g, 83.3 mmol, 1 equiv) in DMF (30 ml) was added *N,N*-dimethylformamide dimethylacetal (35 ml, excess) and the resulting solution was stirred at 45°C for 30 min then cooled to room temperature and concentrated *in vacuo*. Trituration of the residue with Et_2O/*iso*-hexane gave methyl 4-[(*E*)-2-

(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200) (20 g, 81%) as a dark red solid which was used in the next step without further purification.

Description 201

Methyl 4-amino-1*H*-indole-6-carboxylate (D201)

To a solution of methyl 4-[(*E*)-2-(dimethylamino)ethenyl]-3,5-dinitrobenzoate (D200) (10 g, 34 mmol, 1 equiv) in MeOH (250 ml) was added 10% palladium on charcoal (50% wet, 1.0 g, 5% w/w) and the resulting mixture was stirred under an atmosphere of hydrogen for 7 h. The catalyst was removed by filtration through a pad of celite and the solution concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 4-amino-1*H*-indole-6-carboxylate (D201) (5 g, 77%) as a dark pink solid. $[M+H]^+$ = 191.0, RT = 1.20 min.

Description 202

Methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate (D202)

To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (D201) (900 mg, 4,74 mmol, 1 equiv) in DMF (25 ml) at room temperature was added NaH (60% dispersion in mineral oil, 200 mg, 5 mmol, 1.05 equiv) and after 15 min ethyl iodide (400 µl, 5 mmol, 1.05 equiv). The resulting mixture was stirred for 30 min then most of the solvent was removed *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/1) gave an oil which was diluted with Et_2O and treated with a 4N HCl solution in Et_2O. The precipitate obtained was filtrated off to give methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate hydrochloride salt (D202) (800 mg, 66%) as a white solid. $[M+H]^+$ = 219.0,
RT = 2.50 min.

Description 203

Methyl 4-amino-3,5-dinitrobenzoate (D203)

Methyl 4-amino-3,5-dinitrobenzoate (D203) was prepared in an analogous manner to Description 25 from commercially available 4-amino-3,5-dinitrobenzoic acid.
$[M-H]^-$ = 240.1, RT = 2.42 min.

Description 204

Methyl 3,4-diamino-5-nitrobenzoate (D204)

To a solution of methyl 4-amino-3,5-dinitrobenzoate (D203) (3.0 g, 12.4 mmol, 1 equiv) in MeOH (40 ml) and cyclohexane (80 ml) was added 10% palladium on charcoal (50% wet, 2.0 g, 33% w/w) and the resulting mixture was refluxed for 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and washed with DMF. The combined organic phases were concentrated *in vacuo* and the residue triturated with Et_2O/*iso*-hexane to give methyl 3,4-diamino-5-nitrobenzoate (D204) (2.1 g, 80%) as a red solid which was used in the next step without further purification.
$[M+H]^+$ = 212.2, RT = 2.46 min.

Description 205

Methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205)

To a solution of methyl 3,4-diamino-5-nitrobenzoate (D204) (1.5 g, 7.1 mmol, 1 equiv) in DMF (30 ml) at room temperature was added K_2CO_3 (2.2 g, 16.0 mmol, 2.25 equiv) then ethyl iodide (1.28 ml, 16.0 mmol, 2.25 equiv). The resulting suspension was stirred at 60°C for 2 h then ethyl iodide (1 ml, 12.5 mmol, 1.8 equiv) was added and the resulting mixture stirred for another 6 h then cooled to room temperature and partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the organic phase washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205) (0.85 g, 50%) as a red solid which was used in the next step without further purification. $[M+H]^+$ = 240.2, RT = 2.95 min.

Description 206

Methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206)

Methyl 4-amino-3-(ethylamino)-5-nitrobenzoate (D205) (850 mg, 3.55 mmol, 1 equiv) was dissolved in formic acid (20 ml) and the resulting solution was stirred at 100°C for 45 min then cooled to room temperature and diluted with AcOEt (200 ml). The organic phase was washed with a 2N aqueous NaOH solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206) (700 mg, 79%) as a tan solid which was used in the next step without further purification. $[M+H]^+$ = 250.1, RT = 2.41 min.

Description 207

Methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207)

To a solution of methyl 1-ethyl-4-nitro-1*H*-benzimidazole-6-carboxylate (D206) (700 mg, 2.81 mmol, 1 equiv) in MeOH (50 ml) and H_2O (5 ml) was added 10% palladium on charcoal (50% wet, 400 mg, 28% w/w) and NH_4COOH (1.77 g, 28.1 mmol, 10 equiv) and the resulting mixture was stirred at 70°C for 30 min then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the MeOH was removed *in vacuo*. The residue was diluted with AcOEt and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207) (500 mg, 81%) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 220.2, RT = 2.17 min.

Description 208

Methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208)

To a solution of methyl 4-chloro-3,5-dinitrobenzoate (D25a) (5.0 g, 19.2 mmol, 1 equiv) in MeOH (300 ml) was added 2-chloroethylamine hydrochloride (4.64 mg, 40 mmol, 2.1 equiv) and NEt_3 (5.5 ml, 40 mmol, 2.1 equiv) and the resulting mixture was refluxed for 5 min then cooled to room temperature. Most of the solvent was evaporated *in vacuo* and the residue filtered off to give methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208) (9 g, 156%) as a yellow solid which was used in the next step without further purification.
$[M+H]^+$ = 304.1, RT = 3.06 min.

Description 209

Methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209)

To a solution of crude methyl 4-[(2-chloroethyl)amino]-3,5-dinitrobenzoate (D208) (9 g, 19.2 mmol, 1 equiv) in MeOH (75 ml) and cyclohexene (150 ml) was added 10% palladium on charcoal (50% wet, 4.5 g, 25% w/w) and the resulting mixture was refluxed for 3 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the solvent was removed *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous HCl solution and the two layers were separated. The aqueous phase was extracted twice with AcOEt and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/1) gave methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209) (1.5 g, 34%) as a red solid. $[M-H]^-$ = 236.2 ,RT = 2.65 min.

Description 210

Methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210)

Methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210) was prepared from methyl 8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D209) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 266.3, RT = 3.07 min.

Description 211

Methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211)

Methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211) was prepared from methyl 4-ethyl-8-nitro-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D210) in an analogous manner to the process described for Description 207 (D207). $[M+H]^+$ = 236.2, RT = 2.23 min.

Description 212

Ethyl 4-amino-3-nitrobenzoate (D212)

Ethyl 4-amino-3-nitrobenzoate (D212) was prepared in an analogous manner to Description 25 from commercially available 4-amino-3-nitrobenzoic acid using EtOH as solvent instead of MeOH.

Description 213

Ethyl 4-amino-3-bromo-5-nitrobenzoate (D213)

To a solution of ethyl 4-amino-3-nitrobenzoate (D212) (21.0 g, 100 mmol, 1 equiv) in CH_2Cl_2 (500 ml) at room temperature was added bromine (6.7 ml, 130 mmol, 1.3 equiv) and the resulting mixture was refluxed for 4 h then bromine (2 ml, 40 mmol, 0.4 equiv) was added and the resulting mixture refluxed for another 3 h then cooled to room temperature. The organic phase was washed twice with a 10% aqueous $Na_2S_2O_3$ solution and twice with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give ethyl 4-amino-3-bromo-5-nitrobenzoate (D213) (27.1 g, 94%) as a yellow solid which was used in the next step without further purification.

Description 214

Ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214)

To a solution of ethyl 4-amino-3-bromo-5-nitrobenzoate (D213) (27.1 g, 93.1 mmol, 1 equiv) in CH_2Cl_2 (500 ml) at room temperature was added *N,N*-diisopropylethylamine (22 ml, 130 mmol, 1.4 equiv) and trifluoroacetic acid anhydride (15.8 ml, 111.7 mmol, 1.2 equiv) and the resulting mixture was stirred for 2 h. *N,N*-diisopropylethylamine (22 ml, 130 mmol, 1.4 equiv) and trifluoroacetic acid anhydride (15.8 ml, 111.7 mmol, 1.2 equiv) were added and the resulting mixture was stirred for another 2 h. H_2O was added and the two layers were separated. The organic phase was washed twice with a 2N aqueous HCl solution, H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 3/1) gave ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) (29.4 g, 82%) as a yellow solid.

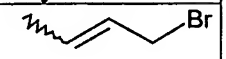
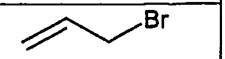
Description 215

Ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215)

To a solution of ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) (12.0 g, 31.3 mmol, 1 equiv) in CH_3CN (100 ml) was added K_2CO_3 (5.6 g, 40 mmol, 1.3 equiv) and 1-bromo-3-methyl-2-butene (5.1 ml, 43.8 mmol, 1.4 equiv) and the resulting mixture was refluxed for 1 h then cooled to room temperature. The precipitate formed was filtered off through a pad of celite and washed with CH_3CN. The combined organic layers were concentrated *in vacuo* and the residue diluted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 4/1) gave ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215) (12.9 g, 91%) as an orange oil.

Descriptions 216-217 (D216-217)

The following compounds were obtained from ethyl 3-bromo-5-nitro-4-[(trifluoroacetyl)amino]benzoate (D214) in an analogous manner using the appropriate allyl bromide:

Description	Allyl bromide
Ethyl 3-bromo-4-[(2*E/Z*)-2-buten-1-yl(trifluoroacetyl)amino]-5-nitrobenzoate (D216)	
Ethyl 3-bromo-5-nitro-4-[2-propen-1-yl(trifluoroacetyl)amino]benzoate (D217)	

Description 218

Ethyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218)

To a solution of ethyl 3-bromo-4-[(3-methyl-2-buten-1-yl)(trifluoroacetyl)amino]-5-nitrobenzoate (D215) (12.9 g, 28.5 mmol, 1 equiv) in DMF (130 ml) were added HCOONa (1.94 g, 28.5 mmol, 1 equiv), Na_2CO_3 (7.54 g, 71.2 mmol, 2.5 equiv), Bu_4NCl (8.7 g, 31.3 mmol, 1.1 equiv) and palladium (II) acetate (320 mg, 1.42 mmol, 0.05 equiv) and the resulting mixture was stirred under nitrogen for 1 h then cooled to room temperature and *concentrated*

in vacuo. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The insoluble material in the aqueous phase was filtered off through a pad of celite and the aqueous layer extracted twice with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218) (10.1 g, 128%) as a black solid which was used in the next step without further purification.

Descriptions 219-220 (D219-220)

The following compounds were obtained in an analogous manner using the appropriate precursor:

Description	Precursor
Ethyl 3-ethyl-7-nitro-1*H*-indole-5-carboxylate (D219)	D216
Ethyl 3-methyl-7-nitro-1*H*-indole-5-carboxylate (D220)	D217

Description 221

Ethyl 7-amino-3-(1-methylethyl)-1*H*-indole-5-carboxylate (D221)

To a solution of crude ethyl 3-(1-methylethyl)-7-nitro-1*H*-indole-5-carboxylate (D218) (10.1 g, 28.5 mmol, 1 equiv) in MeOH (250 ml) and H_2O (25 ml) was added 10% palladium on charcoal (50% wet, 1.5 g, 8% w/w) and NH_4COOH (17 g, 280 mmol, 10 equiv) and the resulting mixture was stirred at 70°C for 3 h then cooled to room temperature. The catalyst was filtered off through a pad of celite and most of the MeOH was removed *in vacuo*. The residue was diluted with AcOEt and the organic layer was washed with a saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 3/1 to 1/1) gave methyl 7-amino-3-(1-methylethyl)-1*H*-indole-5-carboxylate (D221) (1.47 g, 21%) as a white solid.

Descriptions 222-223 (D222-223)

The following compounds were obtained in an analogous manner to the process described for Description 221 using the appropriate precursor:

Description	Precursor
Ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222)	D219
Ethyl 7-amino-3-methyl-1*H*-indole-5-carboxylate (D223)	D220

Descriptions 224-230 (D224-230)

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Description	Precursor	$[M+H]^+$	RT (min)
Ethyl 7-[(4-chlorobutanoyl)amino]-3-methyl-1*H*-indole-5-carboxylate (D224)	D223		
Ethyl 7-[(4-chlorobutanoyl)amino]-3-ethyl-1*H*-indole-5-carboxylate (D225)	D222		
Ethyl 7-[(4-chlorobutanoyl)amino]-3-(1-	D221		

methylethyl)-1*H*-indole-5-carboxylate (D226)			
Methyl 4-[(4-chlorobutanoyl)amino]-1-ethyl-1*H*-benzimidazole-6-carboxylate (D227)	D207		
Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-indole-6-carboxylate (D228)	D201	295.0	2.63
Methyl 4-[(4-chlorobutanoyl)amino]-1-ethyl-1*H*-indazole-6-carboxylate (D229)	D199	324.3	2.70
Methyl 8-[(4-chlorobutanoyl)amino]-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D230)	D211	340.2	2.73

Description 231

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231)

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) was obtained from 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155) in an analogous manner to Description 25 (D25).

Description 232

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) (308 mg, 1.0 mmol, 1 equiv) in CH_2Cl_2 (10 ml) were added NEt_3 (166 µl, 1.2 mmol, 1.2 equiv), bis(1,1-dimethylethyl) dicarbonate (251 mg, 1.15 mmol, 1.15 equiv) and DMAP (12 mg, 0.1 mmol, 0.1 equiv) and the resulting mixture was stirred at room temperature for 30 min. The organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration in Et_2O/*iso*-hexane gave 1-(1,1-dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232) (150 mg, 37%) as a white solid which was used in the next step without further purification. $[M+H+NH_3]^+$ = 426.2, RT = 3.38 min.

Description 233

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233)

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233) was obtained from 1-(1,1-dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-1,6-dicarboxylate (D232) in an analogous manner to the process described for Ester 116 (B116). No molecular ion, RT = 3.23 min.

Description 234

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234)

1-(1,1-Dimethylethyl) 6-methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-1,6-dicarboxylate (D233) (500 mg, 1.2 mmol, 1 equiv) was dissolved in a 4N HCl

solution in Et_2O (10 ml, 40 mmol, excess) and the resulting solution was stirred at room temperature for 1 h then concentrated *in vacuo*. Trituration of the residue with Et_2O gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234) (430 mg, 100%) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 311.0, RT = 2.16 min.

Description 235

Methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate hydrochloride salt (D234) (350 mg, 1.0 mmol, 1 equiv) in AcOEt (5 ml) were added NEt_3 (140 ml, 1.0 mmol, 1 equiv) and acetic anhydride (0.5 ml, 5.6 mmol, 5.6 equiv) and the resulting mixture was stirred at 50°C for 30 min then cooled to room temperature and washed with a 2N aqueous HCl solution followed by a saturated aqueous $NaHCO_3$ solution, then dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235) as a white solid which was used in the next step without further purification. $[M+H]^+$ = 353.2, RT = 2.24 min.

Description 236

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236)

To a solution of methyl 4-amino-1-ethyl-1*H*-indole-6-carboxylate hydrochloride salt (D202) (1.7 g, 6.68 mmol, 1 equiv) in CH_2Cl_2 (50 ml) was added NEt_3 (4.2 ml, 30 mmol, 4.5 equiv) then 3-chloro-1-propanesulfonyl chloride (1.8 ml, 15.0 mmol, 2.2 equiv) and the resulting mixture was stirred for 2 h. The organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236) (1.85 g, 55%) as a light tan solid. $[M-H]^-$ = 498.1, RT = 3.51 min.

Description 237

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indazole-6-carboxylate (D237)

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indazole-6-carboxylate (D237) was obtained from methyl 4-amino-1-ethyl-1*H*-indazole-6-carboxylate in an analogous manner to the process described for methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 500.1, RT = 3.50 min.

Description 238

Methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238)

Methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238) was obtained from methyl 8-amino-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D211) in an analogous manner to the process described for methyl

4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 517.2, RT = 3.32 min.

Description 239

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239)

Methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239) was obtained from methyl 4-amino-1-ethyl-1*H*-benzimidazole-6-carboxylate (D207) in an analogous manner to the process described for methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236). $[M+H]^+$ = 500.3, RT = 3.20 min.

Description 240

4-{[(3-Chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240)

To a solution of methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D236) (1.8 g, 3.6 mmol, 1 equiv) in MeOH (100 ml) was added a 2N aqueous NaOH solution (20 ml, 40 mmol, excess) and the resulting mixture was stirred for 1 h. Most of MeOH was removed *in vacuo* and the residue partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the aqueous phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 4-{[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240) (930 mg, 75%) as a brown oil which was used in the next step without further purification.

Description 241

Methyl 4-{[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D241)

Methyl 4-{[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D241) was obtained from 4-{[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylic acid (D240) in an analogous manner to Description 25 (D25). $[M+H]^+$ = 359.2, RT = 3.12 min.

Description 242

Ethyl 7-{[(4-chlorobutyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D242)

To a solution of ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222) (150 mg, 0.65 mmol, 1 equiv) in CH_2Cl_2 (10 ml) at room temperature were added pyridine (115 µl, 1.42 mmol, 2.2 equiv), 4-chloro-1-butanesulfonyl chloride (D20) (259 mg, 1.36 mmol, 2.1 equiv) and DMAP (8 mg, 0.065 mmol, 0.1 equiv) and the resulting mixture was stirred for 1 h then diluted with AcOEt and washed with a 2N aqueous HCl solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo* to give ethyl 7-{[(4-chlorobutyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D242) (230 mg, 92%) as a purple oil which was used in the next step without further purification. $[M+H]^+$ = 387.3, RT = 3.35 min.

Description 243

Ethyl 7-{[(3-chloropropyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D243)

Ethyl 7-{[(3-chloropropyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D243) was obtained from ethyl 7-amino-3-ethyl-1*H*-indole-5-carboxylate (D222) in an analogous manner to the

process described for Description 242 (D242) using 3-chloro-1-propanesulfonyl chloride instead of 4-chloro-1-butanesulfonyl chloride (D20). $[M+H]^+$ = 373.0, RT = 3.49 min.

Description 244

3,4-Diamino-5-nitrobenzoic acid (D244)

To a solution of 4-amino-3,5-dinitrobenzoic acid (10 g, 44 mmol, 1 equiv) in DME (100 ml) and $CHCl_3$ (10 ml) under nitrogen was added 10% palladium on charcoal (50% wet, 1 g, 5% w/w) and the resulting suspension was stirred under an atmosphere of nitrogen (35 psi) for 15 h. 10% Palladium on charcoal (50% wet, 1 g, 5% w/w) was added and the resulting suspension was stirred under an atmosphere of hydrogen (35 psi) for another 15 h. The catalyst was filtered off through a pad of celite and the solution was concentrated *in vacuo* to give 3,4-diamino-5-nitrobenzoic acid (D244) (9.85 g, 113%) as a red solid which was used in the next step without further purification. $[M-H]^-$ = 196.1, RT = 2.15 min

Description 245

Methyl 3,4-diamino-5-nitrobenzoate (D245)

Methyl 3,4-diamino-5-nitrobenzoate (D245) was prepared in an analogous manner to Description 25 from 3,4-diamino-5-nitrobenzoic acid (D244).$[M+H]^+$ = 212.2, RT = 2.40 min.

Description 246

Methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246)

To a solution of methyl 3,4-diamino-5-nitrobenzoate (D245) (2.5 g, 12 mmol, 1 equiv)in AcOH (10 ml) at room temperature was added $NaNO_2$ (900 mg, 13 mmol, 1.1 equiv) and the resulting mixture was stirred at 60°C for 1 h, cooled to room temperature and concentrated *in vacuo*. the residue was partitioned between AcOEt and a 5% aqueous citric acid solution and the layers were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Trituration of the residue in Et_2O/*iso*-hexane gave methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246) (2.08 g, 78%) as an orange solid which was used in the next step without further purification.

$[M+H]^+$ = 223.3, RT = 2.31 min.

Description 247

Methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247)

Methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247) was obtained from methyl 4-nitro-1*H*-1,2,3-benzotriazole-6-carboxylate (D246) in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150).
$[M+H]^+$ = 193.3, RT = 2.01 min.

Description 248

Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248)

Methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248) was obtained from methyl 4-amino-1*H*-1,2,3-benzotriazole-6-carboxylate (D247) in an analogous manner to the process described for Description 2 (D2). No molecular ion, RT = 3.19 min.

Description 249

Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249)

Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249) was obtained from methyl 4-[(4-chlorobutanoyl)amino]-1*H*-1,2,3-benzotriazole-6-carboxylate (D248) in an analogous manner to the process described for Ester 27 (B27).
$[M+H]^+$ = 261.2, RT = 2.25 min.

Description 250

Methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250)

A solution of methyl 3,4-diamino-5-nitrobenzoate (D245) (1.3 g, 6.16 mmol, 1 equiv) in HCOOH (20 ml) was stirred at 100°C for 1 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous NaOH solution and the layers were separated. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250) (1.5 g, 110%) as a light brown solid which was used in the next step without further purification.
$[M+H]^+$ = 222.3, RT = 2.29 min.

Description 251

Methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251)

Methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251) was obtained from methyl 4-nitro-1*H*-benzimidazole-6-carboxylate (D250) in an analogous manner to the process described for methyl 5-amino-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D150). $[M+H]^+$ = 192.3, RT = 1.55 min.

Description 252

Methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252)

To a solution of methyl 4-amino-1*H*-benzimidazole-6-carboxylate (D251) (1.1 g, 5.76 mmol, 1 equiv) in CH_2Cl_2 (80 ml) at room temperature were added pyridine (1.02 ml, 12.67 mmol, 2.2 equiv), 4-chloro-1-butanesulfonyl chloride (D20) (2.31 g, 12.1 mmol, 2.1 equiv) and DMAP (704 mg, 5.76 mmol, 1 equiv) and the resulting mixture was stirred for 1 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase was washed with a 2N aqueous HCl solution and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 2/3) gave methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252) (1 g, 50%) as a colorless oil. $[M+H]^+$ = 346.1, RT = 2.97 min.

Description 253

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253)

To a solution of methyl 4-{[(4-chlorobutyl)sulfonyl]amino}-1*H*-benzimidazole-6-carboxylate (D252) (1 g, 3.23 mmol, 1 equiv) in EtOH (50 ml) was added NEt_3 (2 ml, excess) and the resulting solution was stirred at 70°C for 2 days. then cooled to room temperature and

concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 5% aqueous citric acid solution. The aqueous phase was saturated with NaCl and extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH: 96/4 to 90/10) gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253) (250 mg, 25%) as a pale yellow solid. $[M+H]^+$ = 310.3, RT = 2.11 min.

Description 254

Methyl 4-hydroxy-3,5-diiodobenzoate (D254)

Methyl 4-hydroxy-3,5-diiodobenzoate (D254) was prepared in an analogous manner to Description 25 (D25) from commercially available 4-hydroxy-3,5-diiodobenzoic acid.

Description 255

Methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255)

To a solution of methyl 4-hydroxy-3,5-diiodobenzoate (D254) (26.9 g, 66.7 mmol, 1 equiv) in acetone (250 ml) at room temperature were added K_2CO_3 (13.8 g, 100 mmol, 1.5 equiv) and 1-bromo-2-butene (8.25 ml, 80 mmol, 1.2 equiv) and the resulting suspension was stirred at 55°C for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two layers were separated. The organic phase was washed with a 2N aqueous NaOH solution and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255) (28.6 g, 94%) as a white solid which was used in the next step without further purification.

Description 256

Methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256)

Methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256) was obtained from methyl 4-hydroxy-3,5-diiodobenzoate (D254) in an analogous manner to the process described for Description 255 (D255) using 3-bromo-1-propene instead of 1-bromo-2-butene.

Description 257

Methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257)

Methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257) was obtained from methyl 4-hydroxy-3,5-diiodobenzoate (D254) in an analogous manner to the process described for Description 255 (D255) using 4-bromo-1-butene instead of 1-bromo-2-butene. $[M+H]^+$ = 458.8, RT = 4.05 min.

Description 258

Methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258)

To a solution of methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3,5-diiodobenzoate (D255) (5 g, 11 mmol, 1 equiv) in toluene (50 ml) were added 2-pyrrolidinone (1.08 g, 13 mmol, 1.2 equiv), K_3PO_4 (4.46 g, 21 mmol, 2 equiv), CuI (105 mg, 0.55 mmol, 0.05 equiv) and dimethyl ethylene diamine (117 µl, 1.1 mmol, 0.1 equiv) and the resulting mixture was stirred at 100°C for 15 h

then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers were separated. The organic phase was dried under $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave methyl 4-[(2*E*/*Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258) (1.4 g, 31%) as a colorless oil. $[M+H]^+$ = 415.9 ,RT = 3.27 min.

Description 259

Methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259)

Methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259) was obtained from methyl 3,5-diiodo-4-(2-propen-1-yloxy)benzoate (D256) in an analogous manner to the process described for Description 258 (D258).

Description 260

Methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260)

Methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260) was obtained from methyl 4-(3-buten-1-yloxy)-3,5-diiodobenzoate (D257) in an analogous manner to the process described for Description 258 (D258). $[M+H]^+$ = 416.0, RT = 3.02 min.

Description 261

Methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261)

Methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261) were obtained from methyl 4-(3-buten-1-yloxy)-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D260) in an analogous manner to the process described for methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163). $[M+H]^+$ = 288.1, RT = min.

Description 262

Methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262)

Methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262) was obtained from methyl 3-bromo-5-iodobenzoate (D8a) in an analogous manner to the process described for Description 17 (D17) using D8a instead of D8b as starting material.

Description 263

Methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263)

Methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263) was obtained from methyl 3-bromo-5-iodobenzoate (D8a) in an analogous manner to the process described for Description 18 (D18) using D8a instead of D8b as starting material.

Description 264

Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate;
Methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate;
Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264)

Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate and methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264) have been obtained from methyl 3-bromo-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D262) in an analogous manner to the process described for Description 73 (D73)

Description 265

Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate; Methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate; Methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265)

Methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate and methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265) have been obtained from methyl 3-bromo-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D263) in an analogous manner to the process described for Description 73 (D73).

Description 266

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266) was obtained from methyl 3-bromo-5-nitrobenzoate (D11) in an analogous manner to the process described for Description 15 (D15) using Description 22b (D22b) instead of Description D22a (D22a).

Description 267

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267)

Methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (D266) in an analogous manner to the process described for Description 16 (D16).

Description 268

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268)

To a solution of methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D267) (7.5 g, 26.4 mol, 1 equiv) in a 2N aqueous HCl solution (75 ml) and MeOH (75 ml) at 0°C was added $NaNO_2$ (4.0 g, 58.1 mmol, 2.2 equiv) portionwise over 20 min. MeOH (50 ml) and H_2O (200 ml) were added and the resulting mixture was stirred at 95°C for 1 h then cooled to room temperature. Most of the MeOH was removed *in vacuo* and the resulting aqueous phase was extracted with AcOEt. The insoluble material was filtered off to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D) (0.63 g, 8%). The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a brown residue which was redissolved in AcOEt. The organic phase was extracted with a saturated aqueous Na_2CO_3 solution and the aqueous phase was extracted three times with Et_2O then acidified to pH 1 and re-extracted three times with AcOEt. The combined organic phases were washed

with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) (2.2 g, 30%).

Description 269

Methyl 5-(1-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(2-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(3-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D269)

Methyl 5-(1-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(2-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate; methyl 5-(3-cyclopenten-1-yl)-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (D269) were obtained from Description 158 (D158) in an analogous manner to the process described for Description 73 (D73)

Description 270

Ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270)

Ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270) was obtained from ethyl [3-(trifluoromethyl)phenyl]acetate in an analogous manner to the process described for Description 98 (D98).

Description 271

2-Methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271)

2-Methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271) was obtained from ethyl 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoate (D270) in an analogous manner to the process described for Description 99 (D99).

Description 272

Phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272)

Phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272) was obtained from 2-methyl-2-[3-(trifluoromethyl)phenyl]propanoic acid (D271) in an analogous manner to the process described for Description 100 (D100).

Description 273

2-({[(1,1-Dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273)

To a solution of 1,1-dimethylethyl (2-hydroxy-1,1-dimethylethyl)carbamate (5.1 g, 27 mmol, 1 equiv) in CH_2Cl_2 (100 ml) at room temperature were added NEt3 (11.3 ml, 81 mmol, 3 equiv) and methanesulfonyl chloride (28.3 mmol, 2.2 ml, 1.05 equiv)and the resulting solution was stirred for 2 h then partitioned between AcOEt and a saturated aqueous $NaHCO_3$ solution. The two layers were separated and the organic phase dried over $MgSO_4$ and concentrated *in vacuo* to give 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) (7.8 g, 108%) as a yellow oil which was used in the next step without further purification.

Description 274

1,1-Dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274)

To a solution of phenol (2.1 g, 22.4 mmol, 3 equiv) in DMF (10 ml) at room temperature were added NaH (60% dispersion in mineral oil, 360 mg, 9.0 mmol, 1.2 equiv) and after 10 min 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) (2 g, 7.5 mmol, 1 equiv) and the resulting solution was stirred at 50°C for 2 h then cooled to room temperature and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9/1 to 6/1) gave 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274) (180 mg, 9%) as a yellow oil.

Description 275

1,1-Dimethylethyl {1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}carbamate (D275)

1,1-Dimethylethyl {1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}carbamate (D275) was prepared from 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) in an analogous manner to 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274) using phenylmethanol instead of phenol.

Description 276

1,1-Dimethylethyl {1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}carbamate (D276)

1,1-Dimethylethyl {1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}carbamate (D276) was prepared from 2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-2-methylpropyl methanesulfonate (D273) in an analogous manner to 1,1-dimethylethyl [1,1-dimethyl-2-(phenyloxy)ethyl]carbamate (D274)using 2-methyl-1-propanethiol instead of phenol.

Description 277

1,1-Dimethylethyl (4,4-difluorocyclohexyl)carbamate (D277)

To a solution of 1,1-dimethylethyl (4-oxocyclohexyl)carbamate (1 g, 4.69 mmol, 1 equiv) in CH_2Cl_2 (15 ml) was added DAST (1.05 ml, 7.98 mmol, 1.7 equiv) and the resulting mixture was stirred for 15 h. A saturated aqueous $NaHCO_3$ solution was added and the resulting biphasic mixture was stirred vigorously for 1 h. The two layers were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phase were dried over $MgSO_4$ and concentrated *in vacuo* to give 1,1-dimethylethyl (4,4-difluorocyclohexyl)carbamate (D277) (1.03 g, 93%) as a beige solid which was used in the next step without further purification.

Descriptions 278-281 (D278-281)

The following acids have been obtained by alkylation of cyclobutanecarboxylic acid as described in: K. Tani, A. Naganawa, A. Ishida, K. Sagawa, H. Harada, M. Ogawa, T. Maruyama, S. Ohuchida, H. Nakai, K. Kondo, M. Toda *Bio. Med. Chem.* **2002**, 10, 1093-1106:

Description
1-Ethylcyclobutanecarboxylic acid (D278)
1-Propylcyclobutanecarboxylic acid (D279)
1-(1-Methylethyl)cyclobutanecarboxylic acid (D280)

1-[(3-Chlorophenyl)methyl] cyclobutanecarboxylic acid (D281)

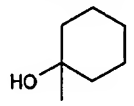
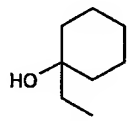
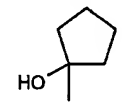
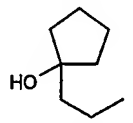
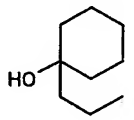
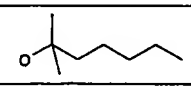
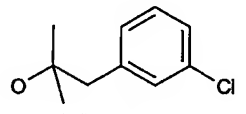
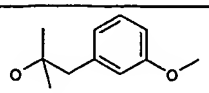
Descriptions 282-285 (D282-285)

The following compounds have been obtained from their precursors in an analogous manner to the process described for Description 100 (D100):

Description	Precursor
Phenylmethyl (1-ethylcyclobutyl) carbamate (D282)	D278
Phenylmethyl (1-propylcyclobutyl) carbamate (D283)	D279
Phenylmethyl [1-(1-methylethyl)cyclobutyl] carbamate (D284)	D280
Phenylmethyl {1-[(3-chlorophenyl)methyl] cyclobutyl}carbamate (D285)	D281

Descriptions 286-293 (D286-293)

The following amides were obtained via a Ritter reaction as described in: M. Mousseron Bull. Soc. Chim. Fr. 1957, 596.:

Description	Precursor
N-(1-Methylcyclohexyl) acetamide (D286)	
N-(1-Ethylcyclohexyl) acetamide (D287)	
N-(1-Methylcyclopentyl) acetamide (D288)	
N-(1-Propylcyclopentyl) acetamide (D289)	
N-(1-Propylcyclohexyl) acetamide (D290)	
N-(1,1-Dimethylhexyl)acetamide (D291)	
N-[2-(3-Chlorophenyl)-1,1-dimethylethyl] acetamide (D292)	
N-{1,1-Dimethyl-2-[3-(methyloxy)phenyl]ethyl}acetamide (D293)	

Description 294

4,4-Dimethylcyclohexanone (D294)

4,4-Dimethylcyclohexanone (D294) was obtained from 4,4-dimethyl-2-cyclohexen-1-one in an analogous manner to the process described for ester 116 (B116).

Description 295

3,3-Dimethylcyclopentanone (D295)

3,3-Dimethylcyclopentanone (D295) was obtained from 4,4-dimethyl-2-cyclopenten-1-one in an analogous manner to the process described for 4,4-dimethylcyclohexanone (D294).

Description 296

4,4-Dimethylcyclohexanone oxime (D296)

To a solution of 4,4-dimethylcyclohexanone (D294) (9.2 g, 73 mmol, 1 equiv) in EtOH (50 ml) and H_2O (50 ml) were added $NH_2OH.HCl$ (6.6 g, 94.5 mmol, 1.3 equiv) and Na_2CO_3 (10.06 g, 94.5 mmol, 1.3 equiv) and the resulting cloudy solution was refluxed for 2 h then cooled to room temperature. Most of EtOH was removed in vacuo and the aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 4,4-dimethylcyclohexanone oxime (D296) (10 g, 97%) as a colourless solid which was used in the next step without purification.

Descriptions 297-298 (D297-298)

The following oxime were obtained for their precursor in an analogous manner to the process described for Description (D296).

Description	Precursor
(1*E/Z*)-2,2-Dimethylcyclohexanone oxime (D297)	D294
(*1E/Z*)-3,3-Dimethylcyclopentanone oxime (D298)	D295

Descriptions 299-311 (D299-311)

The following compounds have been obtained from (2*S*)-2-(1-methylethyl)-3,6-bis(methyloxy)-2,5-dihydropyrazine according to the general procedure described in: P. dalla Croce, C. la Rosa, E. Pizzatti *Tetrahedron: Asymmetry* **2000**, *11*, 2635-2642:

Description
3,5-Difluoro-L-phenylalaninate (D299)
3-Fluoro-L-phenylalaninate (D300)
3,4-Difluoro-L-phenylalaninate (D301)
2-Chloro-L-phenylalaninate (D302)
Methyl-3-chloro-L-phenylalaninate (D303)
Methyl 4-chloro-L-phenylalaninate (D304)
Methyl 3-(2-thienyl)-L-alaninate (D305)
Methyl 3-(3-thienyl)-L-alaninate (D306)
Methyl 3-(2-furanyl)-L-alaninate (D307)
Methyl 3-(2-pyridinyl)-L-alaninate (D308)
Methyl 3-(1,3-thiazol-2-yl)-L-alaninate (D309)
Methyl 3-(1*H*-pyrazol-1-yl)-L-alaninate (D310)
Methyl 3-(3-pyridinyl)-L-alaninate (D311)

Descriptions 312-313 (D312-313)

Descriptions 312-313 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Description	Acid	Amine	$[M+H]^+$	RT (min)
3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (D312)	A117	C16	630.4	2.89
3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (D313)	A117	C14	592.4	2.75

Description 314

1-[3-(Methyloxy)phenyl]cyclohexanol (D314)

To a solution of 3-methoxyphenylmagnesium bromide (1M in THF, 61 ml, 61 mmol, 1 equiv) at 0°C was slowly added cyclohexanone (6g, 61 mmol, 1 equiv) in Et_2O (30 ml). The resulting mixture was stirred at room temperature for 4 h then poured in H_2O at 0°C. The two layers were separated and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give 1-[3-(methyloxy)phenyl]cyclohexanol (D314) (12.4 g, 100%) as a pale yellow oil which was used in the next step without further purification.

Description 315

1-(1-Azidocyclohexyl)-3-(methyloxy)benzene (D315)

To a solution of 1-[3-(methyloxy)phenyl]cyclohexanol (2.93 g, 14.22 mmol, 1 equiv) in CH_2Cl_2 (25 ml) under nitrogen at 0°C was added sodium azide (1.85 g, 28.44 mmol, 2 equiv) then TFA (4.4 ml, 56.89 mmol, 4 equiv) slowly. 40 Ml of CH_2Cl_2 were then added and the resulting suspension was stirred at room temperature for 16 h then partitioned between Et_2O and H_2O. The two layers were separated and the organic phase was washed with H_2O and a 1N aqueous NaOH solution then dried over $MgSO_4$ and concentrated *in vacuo* to give 1-(1-azidocyclohexyl)-3-(methyloxy)benzene (D315) (2.78 g, 85%) as a clear oil which was used in the next step without further purification.

Description 316

(1*E/Z*)-Propanal oxime (D316)

(1*E/Z*)-Propanal oxime was obtained from propanal in a similar manner to the process described for Description 296 (D296).

Description 317

1,1-Dimethylethyl 2-propyn-1-ylcarbamate (D317)

To a solution of 2-propyn-1-amine (2 g, 36.4 mmol, 1 equiv) in CH_2Cl_2 (20 ml) were added NEt_3 (5.3 ml, 38.18 mmol, 1.05 equiv) and bis(1,1-dimethylethyl) dicarbonate (8.32 g, 38.18 mmol, 1.05 equiv). The resulting mixture was stirred at room temperature for 3 h then poured in a 2N aqueous HCl solution. The two layers were separated and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution then dried over $MgSO_4$ and concentrated *in vacuo* to give 1,1-dimethylethyl 2-propyn-1-ylcarbamate (D317) (4.05 g, 72%) as a colourless crystal.

Description G33

((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentyl)-carbamic acid *tert*-butyl ester (G33)

(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (D94) (1.57g, 6.02 mmol, 1 equiv) was refluxed in *iso*-butylamine (10 ml) for 2 h. The solution was concentrated *in vacuo* and the residue purified by flash chromatography on silica gel to give ((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentyl)-carbamic acid *tert*-butyl ester (G33) (1.52g, 84%) as a white solid.

The following compounds were obtained in an analogous manner to Description 96a using the appropriate (commercially available) acid and amine:

Name
((S)-1-Cyclohexylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (G6)
[(S)-1-(3,3-Dimethyl-butylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (G36)

Description G38

((S)-1-Isobutylcarbamoyl-3-methanesulfonyl-propyl)-carbamic acid *tert*-butyl ester (G38)

To ((S)-1-isobutylcarbamoyl-3-methylsulfanyl-propyl)-carbamic acid *tert*-butyl ester (D96) (1.19 g, 3.9 mmol, 1 equiv) in CH_2Cl_2 (25 ml) at 0°C was added *m*-chloroperbenzoic acid (50-55%, 4.0 g, 11.6 mmol, 3 equiv) portionwise. The resulting mixture was stirred 2 h at 0°C then diluted with AcOEt and washed with saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo* to give ((S)-1-isobutylcarbamoyl-3-methanesulfonyl-propyl)-carbamic acid *tert*-butyl ester (G38) (1.06 g, 81%) as a colourless solid.

Description G157

1,1-Dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157)

To a solution of (1*E/Z*)-propanal oxime (D316) (4g, 54.8 mmol, 1 equiv) in CH_2Cl_2 (200 ml) at room temperature was added N-chloro succinamide (7.44 g, 55.8 mmol, 1.02 equiv) and the resulting solution was stirred at this temperature for 2.5 h then NEt_3 (20 ml, excess) was added and the resulting mixture stirred for 2 h. DIPEA (9.52 mmol, 55.8 mmol, 1.02 equiv) and 1,1-dimethylethyl 2-propyn-1-ylcarbamate (D317) (1.34 g, 8.76 mmol, 0.16 equiv) were added and the solution stirred for 48 h then poured into a 1M aqueous HCl solution. The two layers were separated and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution then dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash

chromatography on silicagel (iso-hexane/AcOEt: 4/1 to 3/1) gave 1,1-dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157) (1.28 g, 63%).

Description F5

1,1,5-Trimethyl-hexylamine (F5)

Description F5 was obtained according to S. S. Berg and D. T. Cowling, *J. Chem. Soc.* (C) 1971, 1653-1658.

Description F33

(2S,3R)-2-Amino-3-hydroxy-hexanoic acid isobutyl-amide hydrochloride salt (F33)

(2S,3R)-2-*tert*-Butoxycarbonylamino-3-hydroxy-hexanoic acid methyl ester (G33) (235 mg, 0.86 mmol, 1 equiv) was dissolved in 4M HCl in dioxan (4 ml) and the solution was stirred for 1 h at room temperature then concentrated *in vacuo*. The residue was triturated with Et_2O to give (2S,3R)-2-amino-3-hydroxy-hexanoic acid isobutyl-amide hydrochloride salt (F33) (176 mg, 95%) as a white solid.

The following compounds (as their hydrochloride salts) have been obtained from the appropriate precursors as indicated in the below table according to an analogous manner to that described for Description F33:

Name	Precursor
(S)-2-Amino-*N*-cyclohexyl-propionamide (F6)	G6
(S)-2-Amino-hexanoic acid *iso*butyl-amide (F36)	G36

Description F15

1-(3-Methoxy-phenyl)-1-methyl-ethylamine (F15)

A flask was charged with [1-(3-methoxy-phenyl)-1-methyl-ethyl]-carbamic acid benzyl ester (D100) (1 g, 3.34 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 10% w/w), NH_4COOH (2.1 g, 33 mmol, 10 equiv), EtOH (40 ml) and H_2O (8 ml). The resulting mixture was stirred at 80°C for 2 h, cooled to room temperature and the catalyst was filtered off using a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was diluted with 1N HCl aqueous solution. The aqueous phase was extracted with AcOEt then basified to pH 13 and extracted twice with AcOEt. These combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield 1-(3-methoxy-phenyl)-1-methyl-ethylamine (F15) (290 mg, 53%) as a yellow gum.

Description F40

2-[3-(Trifluoromethyl)phenyl]-2-propanamine (F40)

2-[3-(Trifluoromethyl)phenyl]-2-propanamine (F40) was obtained from phenylmethyl {1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}carbamate (D272) in an analogous manner to the process described for Description F15 (F15).

Description F41

{1-[3-(Methyloxy)phenyl]cyclohexyl}amine (F41)

To a solution of 1-(1-azidocyclohexyl)-3-(methyloxy)benzene (D315) (2.78 g, 12.0 mmol, 1 equiv) in THF (20 ml) at room temperature was added $LiAlH_4$ (1M in THF, 36 ml, 36 mmol, 3 equiv) and the resulting mixture was stirred at this temperature for 4 h. The mixture was then carefully quenched with a 1N aqueous NaOH solution (6 ml, 60 mmol, 1 equiv) then H_2O. The mixture was filtered through a pad of celite then acidified with a 2N aqueous HCl solution (50 ml). The two layers were separated and the pH of the aqueous phase adjusted to 9 using a 2N aqueous NaOH solution. The aqueous phase was extracted three times with Et_2O and the combined organic phase were dried over $MgSO_4$ then concentrated *in vacuo* to give {1-[3-(methyloxy)phenyl]cyclohexyl}amine (F41) (1.55 g, 63%) as a clear oil which was used in the next step without further purification. $[M+H]^+$ = 189.0, RT = 1.90 min.

Descriptions F48, F61, F81 and F110-114

The following amines were obtained from their corresponding amides in an analogous manner to the process described for Description F5 (F5):

Description	Precursor
2-Methyl-2-heptanamine (F48)	D291
2-Methyl-1-[3-(methyloxy)phenyl]-2-propanamine (F61)	D293
1-Methylcyclohexanamine (F81)	D286
1-Methylcyclohexanamine (F110)	D287
1-Methylcyclopentanamine (F111)	D288
1-Propylcyclopentanamine (F112)	D289
1-Propylcyclohexanamine (F113)	D290
1-(3-Chlorophenyl)-2-methyl-2-propanamine (F114)	D292

Description F52

7-(Methyloxy)-1,2,3,4-tetrahydro-1-naphthalenamine (F52)

7-(Methyloxy)-1,2,3,4-tetrahydro-1-naphthalenamine (F52) was obtained from 7-(methyloxy)-3,4-dihydro-1(2*H*)-naphthalenone in an analogous manner to the process described in US Patent 4,132,737.

Descriptions F54-56 and F155

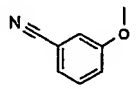
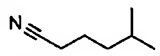
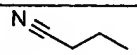
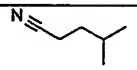
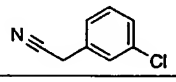
The following amines were prepared from their precursor in an analogous manner to the process described for Amine 1 (C1):

Description	Precursor
2-Methyl-1-[(2-methylpropyl)thio]-2-propanamine hydrogen chloride (F54)	D276
2-Methyl-1-(phenyloxy)-2-propanamine hydrogen chloride (F55)	D274
2-Methyl-1-[(phenylmethyl)oxy]-2-propanamine hydrogen chloride (F56)	D275
4,4-Difluorocyclohexanamine hydrochloride (F155)	D277

Descriptions F63, F73-75 and F77-80

The following amines were prepared from their corresponding nitriles according to the general method described in: P. Bertus, J. Szymoniak *Chem. Comm.*, 2001, 1792:

Description	Precursor

1-[3-(methyloxy)phenyl] cyclopropanamine (F63)	
1-(4-methylpentyl) cyclopropanamine (F73)	
1-ethylcyclopropanamine (F74)	
1-(1-methylethyl) cyclopropanamine (F75)	
1-propylcyclopropanamine (F77)	
1-(3-methylbutyl) cyclopropanamine (F78)	
1-(2-methylpropyl) cyclopropanamine (F79)	
1-[(3-chlorophenyl)methyl] cyclopropanamine (F80)	

Descriptions F69 and F148-150

The following compounds have been obtained from their precursors in an analogous manner to the process described for Description F15 (F15):

Description	Precursor
1-Ethylcyclobutanamine (F69)	D282
1-Propylcyclobutanamine (F148)	D283
1-(1-Methylethyl) cyclobutanamine (F149)	D284
1-[(3-Chlorophenyl)methyl] cyclobutanamine (F150)	D285

Description F70

2-Methyl-1-[(2-methylpropyl)oxy]-2-propanamine (F70)

2-Methyl-1-[(2-methylpropyl)oxy]-2-propanamine (F70) was obtained from 2-Methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71) in an analogous manner to the process described for Ester 166 (B116).

Description F71

2-Methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71)

To a solution of NaH (60% dispersion in mineral oil, 2.0 g, 50 mmol, 1 equiv) in DMF at 0°C was added 2-amino-2-methyl-1-propanol (4.8 ml, 50 mmol, 1 equiv) and after 1 h 3-bromo-2-methyl-1-propene (5.5 ml, 55 mmol, 1.1 equiv). The resulting solution was stirred at room temperature for 15 h then partitioned between AcOEt and H_2O. The two layers were separated and the organic phase was washed with H_2O and brine, dried over $MgSO_4$ and distillated (45°C, P = 150 mbar) to give 2-methyl-1-[(2-methyl-2-propen-1-yl)oxy]-2-propanamine (F71) as a light pink solid.

Description F83

4,4-Dimethylcyclohexanamine (F83)

4,4-Dimethylcyclohexanone oxime (D296) (10 g, 71 mmol, 1 equiv) in EtOH (100 ml) was stirred with Raney Ni (1 g, 10% w/w) under an atmosphere of H_2 (50 psi) for 4 days. The

catalyst was filtered off through a pad of celite and HCl (1M in Et_2O, 100 ml, 100 mmol, 1.4 equiv) were added. The precipitate formed was filtered off and dissolved in water. The aqueous phase was washed with Et_2O and made strongly basic with KOH pellets then extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give 4,4-dimethylcyclohexanamine (F83) (8 g, 89%) as a clear oil which was used in the next step without further purification.

Descriptions F86 and F92

The following amines were obtained from their precursor in an analogous manner to the process described for 4,4-dimethylcyclohexanamine (F83):

Amine	Precursor
2,2-Dimethyl cyclohexanamine (F86)	D297
3,3-Dimethyl cyclopentanamine (F92)	D298

Description F157

[(3-Ethyl-5-isoxazolyl)methyl]amine (F157)

[(3-Ethyl-5-isoxazolyl)methyl]amine (F157) was obtained from 1,1-dimethylethyl [(3-ethyl-5-isoxazolyl)methyl]carbamate (G157) in an analogous manner to the process described in Description F33 (F33).

Preparation of Esters

Ester 1

3-Methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B1)

To a solution of crude 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (D64) (0.17 g, 0.56 mmol, 1 equiv) in THF (2 ml) at 0°C was added portionwise NaH (60% in mineral oil, 24.6 mg, 0.616 mmol, 1.1 equiv) over 2 min. The resulting mixture was stirred at room temperature for 40 min and one drop of MeOH was added to destroy the remaining NaH. The resulting mixture was then diluted with AcOEt, washed sequentially with 2N aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt: 1/1) gave 3-(4-chloro-butanoylamino)-5-methylsulfanyl-benzoic acid methyl ester (B1) (122 mg, 82%) as a white solid. $[M+H]^+ = 266.0$, RT = 2.86 min

Ester 2

3-Ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid ethyl ester (B2)

Ester 2 was prepared from 177 mg (0.54 mmol) of 3-(4-chloro-butanoylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D65) in an analogous manner to that described for Ester 1 which yielded 129 mg (82%) of 3-ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid ethyl ester (B2) as a clear colorless gum after purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 60/40). $[M+H]^+ = 294.1$, RT = 3.23 min

Ester 3

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3)

To a solution of 3-(3-chloro-propane-1-sulfonylamino)-5-methylsulfanyl-benzoic acid methyl ester (D66) (183 mg, 0.54 mmol, 1 equiv) in MeOH (3 ml) was added NEt_3 (150 µl, 1.08 mmol, 2 equiv). The resulting mixture was stirred at 70°C for 2 h then left to cool to room temperature overnight. A further portion of NEt_3 (75 µl, 0.54 mmol, 1 equiv) was added and the mixture was stirred at 80°C for 3 h when another portion of NEt_3 (75 µl, 0.54 mmol, 1 equiv) was added. After another 2 h at 80°C, the solution was cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and 2N aqueous HCl solution. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 60/40) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3) (150 mg, 92%). $[M+H]^+ = 302.0$
RT = 2.89 min

Ester 4

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4)

Ester 4 was prepared from 190 mg (0.52 mmol) 3-(3-chloro-propane-1-sulfonylamino)-5-ethylsulfanyl-benzoic acid ethyl ester (D67) in an analogous manner to that described for Ester 3 which yielded 154 mg (90%) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4) after purification by flash chromatography on silica gel (*iso*-hexane/AcOEt : 60/40). $[M+H]^+ = 330.0$, RT = 3.24 min

Ester 11

3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11)

To 3-hydroxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D37) (0.80 g, 3.4 mmol, 1 equiv) dissolved in DMF (10 ml) was added K_2CO_3 (0.94 g, 6.8 mmol, 2 equiv) and ethyl iodide (1.1 g, 6.8 mmol, 2 equiv). The resulting mixture was heated at 50 °C for 4 h, cooled to room temperature, diluted with 2N aqueous HCl solution (50 ml) and extracted with Et_2O (50 ml). The organic phase was then washed with water (50 ml), dried over $MgSO_4$ and concentrated in *vacuo to* give of 3-ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11) (0.85 g, 95%) as a brown oil which slowly solidified to a tan solid.

Ester 11 (Alternative Procedure)

3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11):

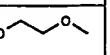
3-(4-Chloro-butanoylamino)-5-ethoxy-benzoic acid methyl ester (D51) (7 g, 20 mmol, 1 equiv) in THF (50 ml) was treated portionwise with NaH (60% in mineral oil, 0.88 g, 22 mmol, 1.1 equiv) over 15 min at room temperature. The resulting mixture was stirred for 30 min and then diluted with AcOEt (300 ml). The resulting solution was washed with 2N aqueous HCl solution (200 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallisation of the residue from Et_2O/hexane gave 3-ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B11) (3.5 g, 66%) as white solid.

The following esters were prepared in an analogous manner to Ester 11 from D37 using an appropriate commercially available reagent:

Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B9)
3-(2-Oxo-pyrrolidin-1-yl)-5-propoxy-benzoic acid methyl ester (B10)
3-Isopropoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B12)
3-(2-Oxo-pyrrolidin-1-yl)-5-pentyloxy-benzoic acid methyl ester (B13)

Ester 14

The following ester was prepared in an analogous manner to Description 38 from Description 37 using the appropriate alcohol indicated in the table below:

Ester	Alcohol
3-(2-Methoxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B14)	

Ester 15

3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15)

3-(3-Benzyloxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D38) in MeOH (15 ml) was hydrogenolysed initially with 10% Pd on charcoal (50% wet, 0.25 g, 0.25 equiv w/w) at atmospheric pressure for 24 hrs and then a further 0.25 g of 10% Pd on charcoal (50% wet, 0.25 g, 0.25 equiv w/w) was added and the mixture hydrogenolysed at 50psi for a further 48 hrs. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane : 1/1) gave 3-(3-hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15) (260 mg, 69% over 2 steps). $[M+H]^+ = 294.0$

Ester 17

3-(3-Methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B17)

3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B15) (127 mg, 0.43 mmol, 1 equiv) in CH_2Cl_2 (2 ml) was treated with proton sponge (279 mg, 1.30 mmol, 3 equiv) and trimethyloxonium tetrafluoroborate (192 mg, 1.30 mmol, 3 equiv). After 3 hrs, further quantities of proton sponge (93 mg, 0.43 mmol, 1 equiv) and trimethyloxonium tetrafluoroborate (65 mg, 0.43 mmol, 1 equiv) were added and stirring was continued for a further 2 h. The mixture was then partitioned between AcOEt and 2N aqueous HCl solution. The two layers were separated and the aqueous phase extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, 2N aqueous HCl solution and brine and then dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on silica gel (ethyl acetate/iso-hexane: 1/4 to 1/3) gave 3-(3-methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B17) (76 mg, 58%). $[M+H]^+ =$ 308.1

Ester 18

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18)

To 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (0.80 g, 3.0 mmol, 1 equiv) dissolved in DMF (10 ml) was added K_2CO_3 (0.94 g, 6.8 mmol, 2 equiv) and

ethyl iodide (1.1g, 6.8 mmol, 2 equiv) and the resulting mixture was heated at 50 °C for 4 h then cooled to room temperature and diluted with 2N aqueous HCl solution (50 ml). The aqueous phase was extracted with Et_2O (50 ml). The organic phase was washed with H_2O (50 ml), dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18) (220 mg, 25%) as a pale yellow oil.

Ester 18 (Alternative Procedure)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18)

A solution of 3-(3-chloro-propane-1-sulfonylamino)-5-ethoxy-benzoic acid methyl ester (D53) (6.7 g, 20 mmol, 1 equiv) in EtOH (100 ml) was treated with NEt_3 (4.0 g, 40 mmol, 2 equiv). The resulting mixture was refluxed for 4 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml) and the resulting solution was washed with 2N aqueous HCl solution (100 ml) followed by saturated aqueous $NaHCO_3$ solution (100 ml) then dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. Crystallisation from Et_2O/hexane gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzoic acid methyl ester (B18) (4.7 g, 78%) as a light tan solid.

Ester 19

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid methyl ester (B19)

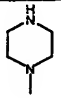
To 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxy-benzoic acid methyl ester (D41) (0.30 g, 1.1 mmol, 1 equiv) dissolved in DMF (5 ml) was added K_2CO_3 (0.306 g, 2.2 mmol, 2 equiv) and 2-iodopropane (374 mg, 2.2 mmol, 2 equiv) and the mixture heated at 50 °C for 4 h then cooled to room temperature and diluted with 2N aqueous HCl solution (50 ml). The aqueous phase was extracted with Et_2O (50 ml) and the organic phase was washed with H_2O (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid methyl ester (B19) (290 mg, 88%) as a pale yellow oil.

The following esters were prepared from Description 41 in an analogous manner to the process described for Ester 19 using the appropriate commercially available reagents:

Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxy-benzoic acid methyl ester (B20)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxy-benzoic acid methyl ester (B21)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentyloxy-benzoic acid methyl ester (B22)

The following esters were prepared in an analogous manner to the process described in Description 30 from the appropriate aryl bromide and amine starting materials listed in the below table:

Ester	Aryl bromide	Amine	$[M+H]^+$	RT (min)
3-(2-Oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid methyl ester (B113)	D9a		289.1	3.03
3-Morpholin-4-yl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B29)	D9a		305.0	2.59

3-(4-Methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B115)	D9a		318.1	1.91
3-(2-Oxo-pyrrolidin-1-yl)-5-piperidin-1-yl-benzoic acid methyl ester (B28)	D9a		303.1	2.93
3-(2-Oxo-piperidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B54)	D10		345.2	3.35
3-Morpholin-4-yl-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B56)	D10		361.2	2.95
3-(2-Oxo-piperidin-1-yl)-5-piperidin-1-yl-benzoic acid *tert*-butyl ester (B55)	D10		359.2	3.35
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B114)	D17		67.1	3.43
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzoic acid *tert*-butyl ester (B61)	D17		383.1	3.04

Ester 24

3,5-Bis-(2-oxo-pyrrolidin-1-yl)benzoic acid methyl ester (B24)

To a solution of 3-bromo-5-iodobenzoic acid methyl ester (D8a) (588 mg, 1.72 mmol, 1.5 equiv) in dioxan (10 ml) was added pyrrolidin-2-one (120 µl, 1.14 mmol, 1 equiv), Cs_2CO_3 (720 mg, 2.21 mmol, 2 equiv), Xantphos (51 mg, 0.09 mmol, 0.08 equiv) and tris(dibenzylideneacetone)dipalladium (0) (28 mg, 0.03 mmol, 0.026 equiv). The reaction mixture was stirred at 100 °C for 16 h, then cooled to room temperature and filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc) yielded 3,5-bis-(2-oxo-pyrrolidin-1-yl)benzoic acid methyl ester (B24) (411 mg, 79%) as light yellow solid.

$[M+H]^+ = 303.2$

The following esters were prepared in an analogous manner to Ester 23 from the appropriate starting materials indicated in the below table:

Ester	Precursor
4-Chloro-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B25)	D28a
4-Methoxy-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B26)	D28b

Ester 27

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27)

To a solution of 3-(4-chloro-butanoylamino)-5-nitro-benzoic acid methyl ester (D2) (56 g, 186 mmol, 1 equiv) in THF (500 ml) under nitrogen was added portionwise NaH (60% w/w in mineral oil, 8 g, 200 mmol, 1.07 equiv) over 10 min. The resulting mixture was stirred at room temperature for 1 h then cooled to 0°C and MeOH was added dropwise until bubbling ceased.

The solution was concentrated *in vacuo* and the residue diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with *iso*-hexane to give 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B27) (38.5 g, 78%) as a light tan solid.

Ester 30

3-(2-Oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid methyl ester (B30)

A flask was charged under nitrogen with 3-bromo-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D9a) (298 mg, 1 mmol, 1 equiv), Cs_2CO_3 (488 mg, 1.5 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (18.3 mg, 0.02 mmol, 0.02 equiv), 2-(di-*tert*-butylphosphino)biphenyl (18 mg, 0.06 mmol, 0.06 equiv) and DME (8 ml). Aniline (136 µl, 1.5 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at 100°C for 16 h then cooled to room temperature, diluted with H_2O and AcOEt. The layers were separated and the aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/1 to 1/1) gave 3-(2-oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid methyl ester (B30) (100 mg, 32%) as a white solid. $[M+H]^+$ = 311.0, RT = 3.14 min

Ester 31

3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B31)

A flask was charged with (benzyl-ethyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D30) (3 g, 7.6 mmol, 1 equiv), 10% Pd on charcoal (50% wet, 600 mg, 10% w/w), NH_4COOH (4.8 g, 76 mmol, 10 equiv), MeOH (30 ml) and H_2O (50 ml). The resulting mixture was stirred at 50°C for 16 h, cooled to room temperature and the catalyst was filtered off using a pad of celite. Most of the MeOH was removed *in vacuo* and the residue was diluted with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B31) (2.2 g, 95%) as a yellow oil. $[M+H]^+$ = 305.2, RT = 3.11 min

The following esters were prepared in an analogous manner to the process described in Ester 31 (B31) from the appropriate benzyl aniline precursor listed in the below table:

Ester	Precursor	$[M+H]^+$	RT (min)
3-Methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32)	D31	291.1	2.96
3-Methylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B57)	D32	249.1 (- *t*Bu)	2.91
3-Ethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid *tert*-butyl ester (B59)	D33	319.2	3.10
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylamino-benzoic acid *tert*-butyl ester (B62)	D34		
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylamino-	D35	355.2	3.32

benzoic acid *tert*-butyl ester (B73)			

Ester 33

Diethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B33)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (100 mg, 0.43 mmol, 1 equiv) in $(CH_2Cl)_2$ (1.5 ml) was added acetaldehyde (0.072 ml, 1.29 mmol, 3 equiv) and sodium triacetoxyborohydride (273 mg, 1.29 mmol, 3 equiv). The resulting solution was stirred at room temperature for 1 h, diluted with AcOEt (20 ml), washed with 2N aqueous NaOH solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give diethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B33) (110 mg, 98%) as a pale yellow oil.

The following esters were prepared in an analogous manner to the process described in Ester 33 (B33) using the appropriate aldehyde and the appropriate aniline indicated in the below table:

Ester	Aniline	$[M+H]^+$	RT (min)
Dimethylamino-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B34)	D4a	263.0	2.63
Diethylamino-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B63)	D16	327.0	2.96
Diethylamino-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B60)	D4b		

Ester 35

3-(2-Oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (500 mg, 2,14 mmol, 1 equiv) in $(CH_2Cl)_2$ (10 ml) was added sodium triacetoxyborohydride (640 mg, 3.02 mmol, 1.4 equiv), propionaldehyde (0.156 ml, 2.14 mmol, 1 equiv) and CH_3COOH (0.125 ml, 2.18 mmol, 1.02 equiv) .The resulting mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (20 ml), washed with saturated aqueous $NaHCO_3$ solution (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 3/2) gave 3-(2-oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35) (250 mg, 42%) as a colourless oil.

The following esters were obtained in an analogous manner to the process described in Ester 35 (B35) using the appropriate aldehyde and the appropriate aniline indicated in the table below:

Ester	Aniline	$[M+H]^+$	RT (min)
3-Benzylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B64)	D16		
3-Butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B65)	D16	327.0	3.10
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methyl-butylamino)-benzoic acid methyl ester (B66)	D16	341.1	3.26

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzoic acid methyl ester (B67)	D16	375.0	3.23
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentylamino-benzoic acid methyl ester (B68)	D16	341.1	3.29
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propylamino-benzoic acid methyl ester (B69)	D16	313.0	2.90
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylamino-benzoic acid methyl ester (B70)	D16	299.0	2.91
3-(Cyclopropylmethyl-amino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B71)	D16	325.0	2.91
3-Isobutylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B36)	D4a	291.1	3.03
3-Benzylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B37)	D4a		
3-(3-Methyl-butylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B38)	D4a		
3-(2-Oxo-pyrrolidin-1-yl)-5-pentylamino-benzoic acid methyl ester (B39)	D4a		
3-Butylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B40)	D4a		
3-(2,2-Dimethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B41)	D4a	305.0	3.22
3-(Cyclopropylmethyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B42)	D4a		
3-(2-Oxo-piperidin-1-yl)-5-propylamino-benzoic acid methyl ester (B58)	D4b		

Ester 43

3-(1-Ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B43)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (200mg, 0.87mmol, 1equiv) in $(CH_2Cl)_2$ (5ml) were added sodium triacetoxyborohydride (1.536 g, 5.22 mmol, 6 equiv), 3-pentanone (0.546 ml, 5.22 mmol, 6 equiv) and AcOH (0.050 ml, 0.87 mmol, 1 equiv). The resulting mixture was stirred at room temperature for 48 h, diluted with CH_2Cl_2 (20ml), washed with saturated aqueous $NaHCO_3$ solution (20ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOH: 3/2) gave 3-(1-ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B43) (106 mg, 40%) as a colourless oil.

$[M+H]^+$ = 305.0

RT = 3.19

The following esters were obtained in an analogous manner to Ester 43 (B43) using the appropriate ketone and the appropriate aniline indicated in the table below:

Ester	Aniline	[M+H]	RT (min)

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzoic acid methyl ester (B72)	D16	313.0	2.82
3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B44)	D4a	227.0	2.75
3-Cyclopentylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B45)	D4a		
3-Cyclohexylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B46)	D4a		

Ester 47

(Acetyl-methyl-amino)-(ethyl-propionyl-amino)-benzoic acid *tert*-butyl ester (B47)

To a solution of 3-methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32) (200 mg, 0.69 mmol, 1 equiv) in CH_2Cl_2 (5 ml) was added NEt_3 (278 µl, 2 mmol, 2.9 equiv) and acetic anhydride (195 µl, 2 mmol, 2.9 equiv). The resulting mixture was stirred at room temperature for 16h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give (acetyl-methyl-amino)-(ethyl-propionyl-amino)-benzoic acid *tert*-butyl ester (B47) (203 mg, 89%) as a pale yellow oil which was used in the next step without further purification.

$[M+H]^+ = 333.1$

RT = 2.76 min

The following esters were prepared in an analogous manner to the process described in Ester 47 from the appropriate amine starting materials:

Ester	Amine
(Acetyl-propyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B48)	B35
(Acetyl-isopropyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B49)	B44

Ester 50

3-Acetylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B50)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (80 mg, 0.34 mmol, 1 equiv) in CH_2Cl_2 (10 ml) was added NEt_3 (0.142 ml, 1.02 mmol, 2 equiv) and acetic anhydride (0.078 ml, 0.82 mmol, 2.4 equiv). The resulting mixture was stirred at room temperature for 16h. The reaction was then diluted with AcOEt (20ml), washed with 2N aqueous HCl solution (20ml), dried over $MgSO_4$, and concentrated *in vacuo* to give 3-acetylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B50) (67 mg, 71%) as a pale yellow foam.

Ester 51

(Methanesulfonyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B51)

To a solution of 3-methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B32) (200 mg, 0.69 mmol, 1 equiv) in CH_2Cl_2 (5 ml) was added NEt_3 (278 µl, 2 mmol, 2.9 equiv) and methanesulphonyl chloride (162 µl, 2 mmol, 2.9 equiv). The resulting mixture was stirred

at room temperature for 16 h, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give (methanesulfonyl-methyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B51) (203 mg, 89%) as a pale yellow oil. $[M+H]^+$ = 313.0, RT = 2.95 min

Ester 52

(Methanesulfonyl-propyl-amino)-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B52)

Ester 52 was prepared from 3-(2-oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid methyl ester (B35) in an analogous manner to that described for Ester 51 (B51).

Ester 53

3-Methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B53)

To a solution of 3-amino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (D4a) (200 mg, 0.85 mmol, 1 equiv) in CH_2Cl_2 (5 ml) and DMF (5 ml) was added NEt_3 (0.181 ml, 1.3 mmol, 1.5 equiv) and methanesulphonyl chloride (0.071 ml, 1 mmol, 1.2 equiv). The resultant mixture was stirred at room temperature for 1 h, diluted with AcOEt (30 ml), washed with 2N aqueous HCl solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O and then filtered to give 3-methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B53) as a pale yellow solid (100 mg, 38%).

Ester 74

5-(2-Oxo-pyrrolidin-1-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (B74)

A solution of 1-*tert*-butyl ester 3-methyl ester (D80) (4.5 g, 12.7 mmol, 1 equiv) in THF (60 ml) was treated portionwise with NaH (60% suspension in mineral oil, 560 mg, 14 mmol, 1.1 equiv) over 5 min at room temperature. The resulting mixture was stirred for 1 h, then MeOH (5 ml) was added and the mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (200 ml) and the organic phase was washed with H_2O (100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid 1-*tert*-butyl ester 3-methyl ester (B74) (3.9 g, 97%) as a white solid.

Ester 76

3-Hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B76)

A suspension of 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) (200 mg, 0.76 mmol, 1 equiv) in THF (20 ml) was cooled to 0 °C and treated with BH_3-Me_2S (2M solution in THF, 0.64 ml, 1.28 mmol, 1.3 equiv). The resulting mixture was refluxed for 1 h and then cooled to room temperature. MeOH (5 ml) was added and the resulting mixture was concentrated *in vacuo*. The residue was diluted with AcOEt (50 ml) and the resulting solution was washed with saturated aqueous $NaHCO_3$ solution (30 ml) and 2N aqueous HCl solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B76) (70 mg, 37%) as a pale yellow oil.

Ester 77

5-(2-Oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid methyl ester (B77)

A suspension of 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) (200 mg, 76 mmol, 1 equiv) in CH_2Cl_2 (20 ml) at room temperature was treated with a few drops of DMF followed by $(COCl)_2$ (100 mg, 0.8 mmol, 1.1 equiv). The resulting mixture was stirred for 1 h and then propylamine (140 mg, 2.4 mmol, 3.3 equiv) was added and the resulting solution was stirred for 30 min. The solution was then washed with 2N aqueous HCl solution (30ml), saturated aqueous $NaHCO_3$ solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid methyl ester (B77) (127 mg, 55%) as a cream waxy solid.

The following compounds were prepared in an analogous manner to that described for Ester 77 from 5-(2-oxo-pyrrolidin-1-yl)-isophthalic acid monomethyl ester (A75) and the appropriate amine:

Ester
N,N-Dimethyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid methyl ester (B78)
N-Methyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid methyl ester (B79)

Ester 80

5-(2-Oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B80)

A solution of 5-(4-chloro-butanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D89) (1.7 g, 4.4 mmol, 1 equiv) THF (20 ml) was treated portionwise with NaH (60% dispersion in mineral oil, 180 mg, 4.5 mmol, 1.1 equiv) and the resulting mixture was stirred for 1 h and then was diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 5-(2-oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B80) (1.38 g, 91%) as a colourless oil.

Ester 81

5-(2-Oxo-piperidin-1-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B81)

Ester 81 was prepared in an analogous manner to Ester 80 from 5-(5-chloro-pentanoylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D90).

Ester 82

3-Nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82)

NaH (60% w/w in mineral oil, 680 mg, 17 mmol, 0.9 equiv) was added portionwise to a solution of 3-(5-chloro-pentanoylamino)-5-nitro-benzoic acid methyl ester (D3) (6 g, 19 mmol, 1 equiv) in THF (40 ml) under nitrogen. The resulting mixture was stirred at room temperature for 1 h and then MeOH was added dropwise. The solution was concentrated *in vacuo* and the residue diluted with AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/*iso*-hexane : 1/2) gave 3-nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid methyl ester (B82) (2.8 g, 53%) as a pale orange oil.

Ester 83

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid methyl ester (B83)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-hydroxymethyl-benzoic acid methyl ester (D84) (400 mg, 1.4 mmol, 1 equiv) in CH_2Cl_2 (40 ml) at 0 °C was treated with (diethylamino)sulfur trifluoride (240 mg, 1.5 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature. The solution was washed with 2N aqueous HCl solution (40 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid methyl ester (B83) (250 mg, 62%) as a white solid.

Ester 84

3-Dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B84)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in EtOH (3 ml) was treated with dimethylamine (33% in EtOH, 3 ml, excess). The resulting mixture was stirred for 15 min and then concentrated *in vacuo* and reevaporated with toluene (5 ml). The residue was dissolved in AcOEt (50 ml) and the resulting solution was washed with saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B84) (170 mg, 99%) as a yellow waxy solid.

Ester 85

3-Azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B85)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in DMF (2 ml) was treated with NaN_3 (39 mg, 0.6 mmol, 1.1 equiv) and the resulting mixture was stirred for 1 h at room temperature and then diluted with AcOEt (50 ml). The resulting solution was washed sequentially with 2N aqueous HCl solution (30 ml), saturated aqueous $NaHCO_3$ solution (30 ml) and H_2O (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give 3-azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B85) as a white solid (129 mg, 76%).

Ester 89

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z)-propenyl-benzoic acid methyl ester (B89)

A suspension of (ethyl)triphenylphosphonium bromide (371 mg, 1.0 mmol, 1.4 equiv) in THF (20 ml) was treated with KO^{t}Bu (112 mg, 1.0 mmol, 1.4 equiv) and the resulting mixture was stirred for 15 min at room temperature. A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) (200 mg, 0.7 mmol, 1 equiv) in THF (10 ml) was added and the resulting mixture was stirred for 1 h at room temperature and then diluted with AcOEt (100 ml). The resulting solution was washed with 2N aqueous HCl solution (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (EtOAc/*iso*-hexane : 1/1) gave 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(E/Z)-propenyl-benzoic acid methyl ester (B89) (135 mg, 65%) as a colourless oil.

The following compounds were prepared in an analogous manner to the process described for Ester 89 from 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-formyl-benzoic acid methyl ester (D86) and the appropriate commercially available starting material:

Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzoic acid methyl ester (B88)
(Z/E)-But-1-enyl-(ethanesulfonyl-ethyl-amino)-benzoic acid methyl ester (B90)
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methyl-propenyl)-benzoic acid methyl ester (B91)

Ester 92

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester (B92)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalic acid monomethyl ester (D83) (750 mg, 2.5 mmol, 1 equiv) in CH_2Cl_2 (30 ml) was treated with 2M $(COCl)_2$ in CH_2Cl_2 (1.5 ml, 3.0 mmol, 1.2 equiv) followed by a few drops of DMF. The resulting mixture was stirred for 30 min and then 32% aqueous ammonia (5 ml, excess) was added. The resulting mixture was stirred for 15 min and then diluted with CH_2Cl_2 (50 ml) and washed with 2N aqueous HCl solution (50 ml). The resulting white precipitate was filtered to give 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester **B92** (650 mg, 87%) as a white solid.

Ester 93

3-Cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B93)

A suspension of 5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid methyl ester (B92) (500 mg, 1.68 mmol, 1 equiv) in CH_2Cl_2 (100 ml) was treated with NEt_3 (404 mg, 4.0 mmol, 2.4 equiv) and trifluoroacetic anhydride (378 mg, 1.8 mmol, 1.1 equiv). The resulting mixture was stirred for 1 h at room temperature and then treated with further portions of NEt_3 (404 mg, 4.0 mmol, 2.4 equiv) and trifluoroacetic anhydride (378 mg, 1.8 mmol, 1.1 equiv) and stirred for another 45 min. The resulting solution was washed with 2N aqueous HCl solution (50 ml), saturated aqueous $NaHCO_3$ solution (50 ml), dried over $MgSO_4$. and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid methyl ester (B93) (350 mg, 75%) as a white solid.

Ester 94

5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B94)

A solution of 5-(3-chloro-propane-1-sulfonylamino)-*N,N*-dipropyl-isophthalamic acid methyl ester (D91) (1.7 g, 4.0 mmol, 1 equiv) in EtOH (20 ml) was treated with NEt_3 (799 mg, 7.9 mmol, 2 equiv) and the mixture was refluxed for 3 h and then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the organic phase was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 5-(1,1-dioxo-1 λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B94) (1.2 g, 78%) as a white solid.

Ester 95

5-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-*N,N*-dipropyl-isophthalamic acid methyl ester (B95)

Ester 95 was prepared in an analogous manner to Ester 94 from 5-(4-chloro-butane-1-sulfonylamino)-*N*,*N*-dipropyl-isophthalamic acid methyl ester (D92).

Ester 100

Fluoro-(2-oxo-pyrrolidin-1-yl)-trifluoromethyl-benzoic acid methyl ester (B100)

3-Bromo-2-fluoro-5-trifluoromethylbenzoic acid methyl ester (D29a) (500 mg, 1.95 mmol, 1 equiv), Cs_2CO_3 (950 mg, 2.92 mmol, 1.5 equiv), pyrrolidin-2-one (248 mg, 2.92 mmol, 1.5 equiv), Xantphos (68 mg, 0.117 mmol, 0.06 equiv) and tris(dibenzylideneacetone)dipalladium (0) (36 mg, 0.039 mmol, 0.02 equiv) were refluxed under argon in dioxan (7 ml) for 18h. After cooling, the mixture was filtered and evaporated *in vacuo*. Purification by flash chromatography on silica gel (AcOEt/iso-hexane : 1/4 to 1/2) gave fluoro-(2-oxo-pyrrolidin-1-yl)-trifluoromethyl-benzoic acid methyl ester (B100) (195 mg, 32%). $[M+H]^+$ 306.2.

The following compounds (Esters 101-102) were prepared in an analogous manner to that described for Description 68 from the appropriate aryl bromide starting material indicated in the below table using the appropriate 2,4,6 trialkenylcyclotriboroxane-pyridine complex as described by F. Kerins and D. F. O' Shea in *J. Org. Chem*, **2002**, *67*, 4968-4971:

Description	Aryl bromide	$[M+H]^+$	RT (min)
3-(2-Methyl-propenyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B101)	D9a	274.1	3.14
3-(2-Oxo-pyrrolidin-1-yl)-5-((E)-styryl)-benzoic acid methyl ester (B102)	D9a		

The following compounds were prepared in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116):

Ester	Alkene	$[M+H]^+$	RT (min)
3-Isopropyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B104)	D71	248.1	2.77
3-(2-Oxo-pyrrolidin-1-yl)-5-propyl-benzoic acid methyl ester (B106)	D72	262.1	3.04
3-Cyclopentyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B107)	D74	288.1	3.26
3-Cyclohexyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B108)	D74		
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propyl-benzoic acid *tert*-butyl ester (B112)	D69		

Ester 109

3-Ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B109)

Ester 109 was prepared in an analogous manner to the process described for Ester 111 from 300 mg (mmol) of 3-(3-hydroxy-3-methyl-but-1-ynyl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (D76) which yielded 220 mg (88%) of 3-ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid *tert*-butyl ester (B109) as an off white solid.

Ester 111

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid *tert*-butyl ester (B111)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-hydroxy-3-methyl-but-1-ynyl)-benzoic acid *tert*-butyl ester (D75) (142 mg, 0.37 mmol, 1 equiv) in toluene (20 ml) was added NaH (60% dispersion in mineral oil, 4 mg, 0.1 mmol, 0.3 equiv). The resulting mixture was stirred at 110°C for 30 min, cooled to room temperature and diluted with AcOEt. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid *tert*-butyl ester (B111) (142 mg, 118%) as a pale yellow oil.

Ester 116

3-(2-Oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116)

To a solution of 3-(2-oxo-piperidin-1-yl)-5-(E/Z)-propenyl-benzoic acid *tert*-butyl ester (D68) (485 mg, 1.5 mmol, 1 equiv) in EtOH (10 ml) and H_2O (2 ml) was added 10% palladium on charcoal (50% wet, 485 mg, 5% w/w) and NH_4COOH (945 mg, 15 mmol, 10 equiv). The resulting mixture was stirred at 65°C for 1h then cooled to room temperature. Most of the EtOH was removed *in vacuo* and the residue dissolved in AcOEt. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116) (300 mg, 70%) as a colorless oil.

Ester 117

Methyl 3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoate (B117)

To a solution of methyl 3-[(3-buten-1-ylsulfonyl)(2-propen-1-yl)amino]-5-propylbenzoate (D135) (1 g, 2.8 mmol, 1 equiv) in CH_2Cl_2 (200 ml) was added bis(tricyclohexylphosphino)benzylidene ruthenium (IV) dichloride(117 mg, 0.14 mmol, 0.05 equiv) and the resulting solution was stirred at room temperature for 48 h then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 9:1) gave methyl 3-(1,1-dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoate (B117) (700 mg, 76%) as a pale purple oil. $[M+H]^+$ = 324.4, RT = 3.10 min.

Ester 118

Methyl 5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (B118)

To a solution of methyl 5-(ethyl{[4-(methyloxy)phenyl]methyl}amino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (D155) (7 g, 17.5 mmol, 1 equiv) in EtOH (150 ml) was added 10% palladium on charcoal (50% wet, 1.4 g, 10% w/w) and the resulting mixture was stirred under an atmosphere of hydrogen (1 atm) for 3 h. The catalyst was filtered off through a pad of celite and the solution concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzoate (B118) (4.8 g, 98%) as a

pale greenish solid which was used in the next step without further purification. $[M+H]^+$ = 281.2, RT = 2.35 min.

The following esters have been obtained from the appropriate precursor in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde.

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzoate (B119)	D152	331.2	2.80
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzoate (B122)	D151	317.1	2.64
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-(methyloxy)benzoate (B139)	D153	343.2	2.64

The following compounds were prepared in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116) from their appropriate precursor:

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzoate (B120)	D159	280.2	2.73
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-propylbenzoate (B173)	D161	330.2	2.91
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-5-propylbenzoate (B174)	D160	-	2.74

Ester 121

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzoate (B121)

1,1-Dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzoate (B121) was prepared from 1,1-dimethylethyl 3-(2-oxo-5-phenyl-1-piperidinyl)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D192) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116). $[M+H]^+$ = 394.3, RT = 3.88 min.

Ester 123

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123)

A flask was charged under nitrogen with methyl 3-bromo-5-nitrobenzoate (D11) (136 mg, 0.52 mmol, 1,1 equiv) , Cs_2CO_3 (216 mg, 0.66 mmol, 1.4 equiv), tris(dibenzylideneacetone)dipalladium(0) (22 mg, 0.023 mmol, 0.05 equiv), Xantphos (27 mg, 0.047 mmol, 0.1 equiv) and toluene (10 ml). 4-phenyltetrahydro-2*H*-1,2-thiazine 1,1-dioxide (J. Morris, D. G. Wishka *J. Org. Chem.* **1991**, *56*, 3549-3556, 100 mg, 0.47 mmol, 1 equiv) was then added and the resulting mixture was stirred at 120°C for 5 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between H_2O and AcOEt and the aqueous phase was re-extracted with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash

chromatography on silica gel (*iso*-hexane/AcOEt : 7/3) gave methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123) (110 mg, 60%) as a yellow oil. $[M+H+NH_3]^+$ = 408.3, RT = 3.24 min

Ester 124

Methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124)

Methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124) was obtained from methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoate (B123) in an analogous manner to the process described for Description 16 (D16). $[M+H]^+$ = 361.3, RT = 2.91 min

Ester 125

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoate (B125)

Methyl 3-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoate (B125) was obtained from methyl 3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B124) in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 389.4, RT = 3.23 min

Ester 126

Methyl 3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B126)

Methyl 3-cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (B126) was obtained from methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate and methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D265) in an analogous manner to the process described for Ester 107 (B107).

Ester 127

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoate (B127)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoate (B127) was obtained from methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoate (D194) in an analogous manner to the process described for Ester 35 (B35) using acetone instead of propionaldehyde. $[M+H]^+$ = 327.2, RT = 2.82 min.

Ester 128

1,1-Dimethylethyl 3-[ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoate (B128)

1,1-Dimethylethyl 3-[ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoate (B128) was obtained from 1,1-dimethylethyl 3-(methylamino)-5-(2-oxo-1-pyrrolidinyl)benzoate (B32) in an analogous manner to the process described in Ester 35 (B35) using acetaldehyde instead of propionaldehyde. $[M+H]^+$ = 319.4, RT = 3.17 min.

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Ester 35 (B35) using acetaldehyde instead of propionaldehyde and the appropriate precursor indicated in the below table.

Ester	Precursor	$[M+H]^+$	RT (min)
Methyl 3-(ethylamino)-4-methyl-5-(2-oxo-1-pyrrolidinyl) benzoate (B129)	D184	277.1	2.63
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-methylbenzoate (B130)	D186	313.1	2.79
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoate (B131)	D188	327.1	2.93
Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-(methyloxy) benzoate (B132)	D187	343.1	2.90
Methyl 3-(ethylamino)-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl) benzoate (B133)	D183	293.1	2.64
Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-(methyloxy) benzoate (B134)	D185	329.1	2.79

Ester 135

Methyl 3-(diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (B135)

Methyl 3-(diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (B135) was obtained as a by-product during the synthesis of methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoate (B131) from methyl 3-amino-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoate (D188).
$[M+H]^+$ = 355.1, RT = 2.95 min.

Ester 136

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (B136)

To a solution of methyl 3-{[(4-chlorobutyl)sulfonyl]amino}-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (D170) (650 mg, 1.72 mmol, 1 equiv) in EtOH (50 ml) was added NEt_3 (500 µl, 3.6 mmol, 2.1 equiv) and the resulting solution was refluxed for 6 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution and a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt: 3/1) gave methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoate (B136) (450 mg, 77%) as a pale yellow oil. $[M+H]^+$ = 340.0, RT = 3.14 min.

Ester 138

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(2-oxo-1-pyrrolidinyl)benzoate (B138)

Methyl 3-(1,1-dioxido-2-isothiazolidinyl)-5-(2-oxo-1-pyrrolidinyl)benzoate (B138) was obtained from methyl 3-[(4-chlorobutanoyl)amino]-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D195) in an analogous manner to the process described for Ester 27 (B27). $[M+H]^+$ = 339.0, RT = 2.41 min.

Ester 140

Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B140)

To a solution of methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B154) (500 mg, 1.94 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 84 mg, 2.1 mmol, 1.1 equiv) and the resulting mixture was stirred 15 min. Ethyl iodide (200 µl, 2.5 mmol, 1.3 equiv) was added and the resulting solution was stirred for 30 min then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/4 to 1/1) gave methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B140) (400 mg, 72%) as an off-white solid. $[M+H]^+$ = 287.0, RT = 2.73 min.

The following compounds have been obtained from their corresponding precursors in an analogous manner to the process described for Description 2 (D2):

Ester	Precursor	$[M+H]^+$	RT (min)
Ethyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B141)	D225		
Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-benzimidazole-6-carboxylate (B149)	D227		
Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indazole-6-carboxylate (B152)	D229	288.4	2.20
Methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B154)	D228	259.0	2.22
Ethyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B160)	D224		
Ethyl 3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B161)	D226		
Methyl 4-ethyl-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B171)	D230	304.3	2.52

Ester 142

Ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B142)

To a solution of ethyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B141) (658 mg, 2.3 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol, 1.3 equiv) and the resulting mixture was stirred 15 min at this temperature. Ethyl iodide (187 µl, 3.0 mmol, 1.3 equiv) was added and the resulting solution was stirred for 30 min then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The

residue was triturated with *iso*-hexane to give ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (620 mg, 90%) as a yellow solid which was used in the next step without further purification.

Ester 143

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143)

To a solution of methyl 4-{[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indole-6-carboxylate (D241) (900 mg, 2.5 mmol, 1 equiv) in EtOH (100 ml) was added NEt_3 (1 ml, 7.3 mmol, 3 equiv) and the resulting solution was refluxed for 1.5 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143) (386 mg, 48%) as a brown oil which was used in the next step without further purification.

Ester 144

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144)

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144) was obtained from ethyl 7-{[(3-chloropropyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D243) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylate (B143). $[M+H]^+$ = 337.1, RT = 3.23 min

Ester 145

Methyl 4-(1,1-dioxIdotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylate (B145)

To a solution of methyl 1-acetyl-4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2,3-dihydro-1*H*-indole-6-carboxylate (D235) (300 mg, 0.85 mmol, 1 equiv) in THF (20 ml) at room temperature was added BH_3 (1.5 M in THF, 2 ml, 3 mmol, 3.5 equiv) and the resulting mixture was stirred at room temperature for 15 h. EtOH (5 ml) was added and the resulting mixture was concentrated *in vacuo* after 5 min. The residue was partitioned between a 2N aqueous HCl solution (20 ml) and CH_2Cl_2 (20 ml) and the biphasic mixture was vigorously stirred for 3 h. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/2) gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylate (B145) (200 mg, 70%) as a very pale yellow solid. $[M+H]^+$ = 339.2, RT = 2.92 min.

Ester 146

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylate (B146)

Ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylate (B146) was prepared from ethyl 7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylate (B144) in an analogous manner to the process described for Ester 142 (B142).

Ester 147

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylate (B147)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylate (D231) (180 mg, 0.58 mmol, 1 equiv) in DMF (3 ml) at room temperature was added NaH (60% dispersion in mineral oil, 24 mg, 0.6 mmol, 1 equiv) and the resulting mixture was stirred 15 min at this temperature. Ethyl iodide (64 µl, 0.8 mmol, 1.4 equiv) was added and the resulting solution was stirred for 1 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel gave methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylate (B147) (110 mg, 51%) as a yellow solid which was used in the next step without further purification. $[M+H]^+$ = 337.0 ,RT = 2.82 min.

Ester 148

Ethyl 7-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylate (B148)

To a solution of ethyl 7-{[(4-chlorobutyl)sulfonyl]amino}-3-ethyl-1*H*-indole-5-carboxylate (D242) (230 mg, 0.59 mmol, 1 equiv) in EtOH (10 ml) was added NEt_3 (249 µl, 1.78 mmol, 3 equiv) and the resulting solution was stirred at 70°C for 3 h. NEt_3 (1 ml, excess) was added and the solution was stirred at the same temperature for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 3/7) gave ethyl 7-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylate (B148) (150 mg, 72%) as a colorless oil. $[M-H]^-$ = 349.3, RT = 3.10 min.

Ester 150

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B150)

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B150) was obtained from methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-benzimidazole-6-carboxylate (D239) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153)
$[M+H]^+$ = 324.5, RT = 2.10 min.

Ester 151

Methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B151)

To a solution of methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-benzimidazole-6-carboxylate (D253) (230 mg, 0.74 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 33 mg, 0.82 mmol, 1.1 equiv) and the resulting mixture was stirred 5 min at this temperature. Ethyl iodide (66 µl, 0.82 mmol, 1.1 equiv) was added and the resulting solution was stirred for 30 min at 60°C then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and a

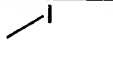
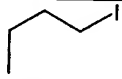
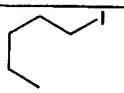
5% aqueous citric acid solution. The two layers were separated and the aqueous phase saturated with NaCl and extracted twice with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give methyl 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylate (B151) (400 mg, 160%) as a pale yellow viscous oil which was used in the next step without further purification. $[M+H]^+$ = 338.1, RT = 2.43 min.

Ester 153

Methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153)

To a solution of methyl 4-{bis[(3-chloropropyl)sulfonyl]amino}-1-ethyl-1*H*-indazole-6-carboxylate (D237) (1.5 g, 3 mmol, 1 equiv) in EtOH (20 ml) was added NEt_3 (920 µl, 6.6 mmol, 2.2 equiv) and the resulting solution was refluxed for 3 h then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with a 2N aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with AcOEt/*iso*-hexane to give methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153) as a light brown solid which was used in the next step without further purification. $[M+H]^+$ = 324.5, RT = 2.35 min.

The following compounds have been obtained from Ester 154 (B154) in an analogous manner to the process described for Ester 140 (B140) using the appropriate alkylating reagent:

Ester	Alkylating reagent	[M+H]+	RT (min)
Methyl 1-methyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B156)		273.0	2.52
Methyl 1-butyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylate (B157)		315.1	3.10
Methyl 4-(2-oxo-1-pyrrolidinyl)-1-pentyl-1*H*-indole-6-carboxylate (B158)			

Ester 159

Methyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B159)

Methyl 3-methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B159) was obtained from methyl 3-iodo-5-(2-oxo-1-pyrrolidinyl)-4-(2-propen-1-yloxy)benzoate (D259) in an analogous manner to the process described for Ester 163 (B163).
$[M+H]^+$ = 274.0, RT = 2.97 min.

Ester 162

Ethyl 1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B162)

Ethyl 1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B162) has been obtained from ethyl 3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B161) using an analogous procedure to the process described for ethyl 3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B142).

Ester 163

Methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163)

To a solution of methyl 4-[(2*E/Z*)-2-buten-1-yloxy]-3-iodo-5-(2-oxo-1-pyrrolidinyl)benzoate (D258) (1.4 g, 3.37 mmol, 1 equiv) in DMF (20 ml) at room temperature under nitrogen were added $Pd(OAc)_2$ (38 mg, 0.17 mmol, 0.05 equiv), NaCOOH (688 mg, 10.1 mmol, 3 equiv), Na_2CO_3 (893 mg, 8.4 mmol, 2.5 equiv) and NBu_4Cl (845 mg, 3.71 mmol, 1.1 equiv). The resulting suspension was stirred under nitrogen at 120°C for 1 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the two phases were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/AcOEt : 1/1) gave methyl 3-ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylate (B163) (250 mg, 26%) as a white solid. $[M+H]^+$ = 288.1, RT = 3.02 min.

Ester 164

Methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethyl)benzoate (B164)

Methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethyl)benzoate (B164) was obtained from methyl 4-methyl-8-(2-oxo-1-pyrrolidinyl)-2*H*-chromene-6-carboxylate and methyl 4-(ethyloxy)-3-[ethyl(propanoyl)amino]-5-(1-methylethenyl)benzoate (D261) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116).

Ester 165

Ethyl 3-ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylate (B165)

To a solution of ethyl 3-ethyl-7-iodo-1*H*-indole-5-carboxylate (D190) (1 g, 2.91 mmol, 1 equiv) in toluene (10 ml) were added 2-piperidinone (346 mg, 3.50 mmol, 1.2 equiv), K_3PO_4 (1.24 g, 5.83 mmol, 2 equiv), CuI (56 mg, 0.29 mmol, 0.1 equiv) and dimethyl ethylene diamine (62 µl, 0.58 mmol, 0.2 equiv) and the resulting mixture was stirred at 100°C for 15 h then cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers were separated. The organic phase was dried under $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 1/0) gave ethyl 3-ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylate (B165) (250 mg, 27%) as an off-white solid.
$[M+H]^+$ = 315.4, RT = 2.98 min.

Ester 166

Ethyl 3-ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B166)

Ethyl 3-ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylate (B166) was obtained from ethyl 3-ethyl-7-iodo-1*H*-indole-5-carboxylate (D166) in an analogous manner to the process described for 1,1-dimethylethyl 3-bromo-5-(2-oxo-5-phenyl-1-piperidinyl)benzoate (D190) using 4-phenyl-2-pyrrolidinone (Koelsch *J. Am. Chem. Soc.* **1943**, (65), p 2093) instead of 5-phenyl-2-piperidinone. $[M+H]^+$ = 377.2, RT = 3.60 min.

Ester 167

Methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (B167)

To a solution of ethyl methyl 4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (D249) (400 mg, 1.54 mmol, 1 equiv) in DMF (10 ml) at room temperature was added NaH (60% dispersion in mineral oil, 68 mg, 1.69 mmol, 1.1 equiv) and the resulting mixture was stirred 5 min at this temperature. Ethyl iodide (135 µl, 1.69 mmol, 1.1 equiv) was added and the resulting solution was stirred for 2 h then concentrated *in vacuo*. The residue was dissolved in AcOEt and the organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (AcOEt/*iso*-hexane: 100/0) gave methyl 1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylate (270 mg, 61%) as a pale yellow oil.

$[M+H]^+$ = 289.3, RT = 2.47 min.

Ester 168

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoate (B168)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoate (B168) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) in an analogous manner to the process described for Ester 18 (B18) from Description 41 (D41).

Ester 169

Methyl 3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (B169)

Methyl 3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (B169) was obtained from methyl 3-(3-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate, methyl 3-(2-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate and methyl 3-(1-cyclopenten-1-yl)-5-(1,1-dioxido-2-isothiazolidinyl)benzoate (D264) in an analogous manner to the process described for Ester 107 (B107).

Ester 170

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoate (B170)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoate (B170) was obtained from methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-hydroxybenzoate (D268) in an analogous manner to the process described for Ester 18 (B18) from Description 41 (D41) using 2-iodopropane instead of iodoethane.

Ester 172

Methyl 8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B172)

Methyl 8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (B172) was obtained from methyl 8-{bis[(3-chloropropyl)sulfonyl]amino}-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylate (D238) in an analogous manner to the process described for methyl 4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylate (B153). $[M+H]^+$ = 340.2 ,RT = 3.32 min.

Ester 175

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoate (B175)

Methyl 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoate (B175) was obtained from Description 152 (D152) in an analogous manner to the process described for Ester 43 (B43) using acetone instead of 3-pentanone.

Ester 176

Methyl 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (B176)

Methyl 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoate (B176) was obtained from Description (D269) in an analogous manner to the process described for Ester B116 (B116).

Preparation of Epoxides

Epoxide K1

1,1-Dimethylethyl {(1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K1)

1,1-Dimethylethyl {(1*S*)-2-(3,5-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K1) was obtained from 3,5-difluoro-L-phenylalaninate (D299) according to the procedure described in Patent US 2003/0004360 A1

The following epoxides were obtained in an analogous manner to the process described for epoxide K1 using the appropriate alaninate:

Epoxide	Precursor
1,1-dimethylethyl {(1*S*)-2-(3-fluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K2)	D300
1,1-dimethylethyl {(1*S*)-2-(3,4-difluorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K3)	D301
1,1-dimethylethyl {(1*S*)-2-(2-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K4)	D302
1,1-dimethylethyl {(1*S*)-2-(3-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K5)	D303
1,1-dimethylethyl {(1*S*)-2-(4-chlorophenyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K6)	D304
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(2-thienyl)ethyl]carbamate (K7)	D305
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(3-thienyl)ethyl]carbamate (K8)	D306
1,1-dimethylethyl {(1*S*)-2-(2-furanyl)-1-[(2*S*)-2-oxiranyl]ethyl}carbamate (K9)	D307
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(2-pyridinyl)ethyl]carbamate (K10)	D308
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(1,3-thiazol-2-yl)ethyl]carbamate (K11)	D309
1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(1*H*-pyrazol-1-yl)ethyl]carbamate (K12)	D310

1,1-dimethylethyl [(1*S*)-1-[(2*S*)-2-oxiranyl]-2-(3-pyridinyl)ethyl]carbamate (K13)	D311

Preparation of BOC-protected amines

BOC-protected amine 1 (H1)

((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H1)

((S)-(S)-1-Oxiranyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester (D101) (10 g, 38 mmol, 1 equiv) [Chirex 1819W94 Lot#9924382] was dissolved in EtOH (100 ml) and cyclohexylamine (13 ml, 114 mmol, 3 equiv) was added. The resulting mixture was heated, under an atmosphere of nitrogen, for 12 h at reflux temperature. The mixture was cooled and the solvent was removed by evaporation *in vacuo*. The resulting white solid was washed with H_2O and then with Et_2O before drying *in vacuo* to give ((1S,2R)-1-benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H1) (9.0 g, 66%). $[M+H]^+ = 363.2$

BOC-protected amines H2-H20, H24-H33 and H36 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (unless amines are commercially available):

BOC-protected amine	Precursor
((1S,2R)-1-Benzyl-3-cyclobutylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H2)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-isobutylamino-propyl)-carbamic acid *tert*-butyl ester (H3)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-propylamino-propyl)-carbamic acid *tert*-butyl ester (H4)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(1,1,5-trimethyl-hexylamino)-propyl]-carbamic acid *tert*-butyl ester (H5)	F5
[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H6)	F6
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(R)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H7)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methyl-1-phenyl-ethylamino)-propyl]-carbamic acid *tert*-butyl ester (H8)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methyl-butylamino)-propyl]-carbamic acid *tert*-butyl ester (H9)	-
((1S,2R)-1-Benzyl-3-*tert*-butylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H10)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H11)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(2,2,3,3,3-pentafluoro-propylamino)-propyl]-carbamic acid *tert*-butyl ester (H12)	-
[(1S,2R)-1-Benzyl-3-(2,2,3,3,4,4,4-heptafluoro-butylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H13)	-

[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H14)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H15)	F15
[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H16)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H17)	-
{(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxy-phenyl)-ethylamino]-propyl}-carbamic acid *tert*-butyl ester (H18)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(5-methyl-hexylamino)-propyl]-carbamic acid *tert*-butyl ester (H19)	-
[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H20)	-
((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H24)	-
[(1S,2R)-1-Benzyl-3-(bis-trifluoromethyl-benzylamino)-2-hydroxy-propyl]-carbamic acid *tert*-butyl ester (H25)	-
((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (H26)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H27)	-
((1S,2R)-1-Benzyl-2-hydroxy-3-isopropylamino-propyl)-carbamic acid *tert*-butyl ester (H28)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxy-benzylamino)-propyl]-carbamic acid *tert*-butyl ester (H29)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-phenyl-ethylamino)-propyl]-carbamic acid *tert*-butyl ester (H30)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((R)-1-phenyl-ethylamino)-propyl]-carbamic acid *tert* butyl ester (H31)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H32)	-
[(1S,2R)-1-Benzyl-2-hydroxy-3-((R)-2-hydroxy-1-isobutylcarbamoyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H33)	F33
[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-isobutylcarbamoyl-pentylamino)-propyl]-carbamic acid *tert*-butyl ester (H36)	F36

BOC-protected amines H40-H114 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (unless amines are commercially available):

BOC-protected amine	Precursor
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-	F40

(trifluoromethyl)phenyl]methyl} amino)propyl]carbamate (H40)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({1-[3-(methyloxy)phenyl]cyclohexyl} amino)-1-(phenylmethyl)propyl]carbamate (H41)	F41
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-1-(phenylmethyl)propyl]carbamate (H42)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]carbamate (H43)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H44)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,3,3-tetramethylbutyl)amino] propyl}carbamate (H45)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H46)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({[4-fluoro-3-(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H47)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H48)	F48
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[2-methyl-5-(trifluoromethyl)phenyl] methyl}amino)-1-(phenylmethyl)propyl]carbamate (H49)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*S*)-2,3-dihydro-1*H*-inden-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H50)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[(1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H51)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[6-(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H52)	F52
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]amino}-1-(phenylmethyl)propyl]carbamate (H53)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methylpropyl)thio] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H54)	F54
1,1-dimethylethyl [(1*S*,2*R*)-3-{[1,1-dimethyl-2-(phenyloxy)ethyl] amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H55)	F55
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(phenylmethyl)oxy] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H56)	F56
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[3-(methyloxy)phenyl] amino}-1-(phenylmethyl)propyl] carbamate (H57)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)propyl]carbamate (H58)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethyl-2-phenylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H59)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[2-(1-naphthalenyl) ethyl]amino}-1-(phenylmethyl) propyl]carbamate (H60)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[3-(methyloxy)phenyl] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H61)	F61

1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(phenylamino)-1-(phenylmethyl)propyl]carbamate (H62)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({1-[3-(methyloxy) phenyl]cyclopropyl}amino)-1-(phenylmethyl)propyl]carbamate (H63)	F63
1,1-dimethylethyl [(1*S*,2*R*)-3-[(cyclohexylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H64)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]propyl}carbamate (H65)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-thiopyran-4-ylamino)propyl]carbamate (H66)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylpropyl)amino]-1-(phenylmethyl)propyl]carbamate (H67)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[4-(1,1-dimethylethyl)cyclohexyl] amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H68)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclobutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H69)	F69
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methylpropyl)oxy] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H70)	F70
1,1-dimethylethyl [(1*S*,2*R*)-3-({1,1-dimethyl-2-[(2-methyl-2-propen-1-yl)oxy]ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H71)	F71
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*R*)-2,3-dihydro-1*H*-inden-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H72)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[1-(4-methylpentyl)cyclopropyl]amino}-1-(phenylmethyl)propyl]carbamate (H73)	F73
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclopropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H74)	F74
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[1-(1-methylethyl)cyclopropyl] amino}-1-(phenylmethyl)propyl]carbamate (H75)	F75
1,1-dimethylethyl [(1*S*,2*R*)-3-(butylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H76)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclopropyl)amino]propyl} carbamate (H77)	F77
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[1-(3-methylbutyl) cyclopropyl]amino}-1-(phenylmethyl)propyl]carbamate (H78)	F78
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[1-(2-methylpropyl) cyclopropyl]amino}-1-(phenylmethyl)propyl]carbamate (H79)	F79
1,1-dimethylethyl [(1*S*,2*R*)-3-({1-[(3-chlorophenyl)methyl] cyclopropyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H80)	F80
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclohexyl) amino]-1-(phenylmethyl)propyl] carbamate (H81)	F81
1,1-dimethylethyl [(1*S*,2*R*)-3-[(2*S*)-bicyclo[2.2.1]hept-2-ylamino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H82)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(4,4-dimethylcyclohexyl)amino]-2-hydroxy-1-	F83

(phenylmethyl)propyl] carbamate (H83)	
1,1-dimethylethyl ((1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-{[(1*R*)-1,2,2-trimethylpropyl]amino} propyl)carbamate (H84)	
1,1-dimethylethyl ((1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-{[(1*S*)-1,2,2-trimethylpropyl]amino} propyl)carbamate (H85)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(2,2-dimethylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H86)	F86
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(pentylamino)-1-(phenylmethyl)propyl]carbamate (H87)	
1,1-dimethylethyl [(1*S*,2*R*)-3-(hexylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H88)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H89)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,1-dimethylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H90)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(cyclopropylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H91)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(3,3-dimethylcyclopentyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H92)	F92
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-(methylamino)-1-(phenylmethyl)propyl]carbamate (H93)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)propyl]carbamate (H94)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(1,2,3,4-tetrahydro-1-naphthalenylamino)propyl] carbamate (H95)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H96)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[4-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H97)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({2-[2-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]carbamate (H98)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(2-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H99)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H100)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(4-chlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H101)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[2-(4-methylphenyl)ethyl]amino}-1-(phenylmethyl)propyl]carbamate (H102)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[2-(2-methylphenyl)ethyl]amino}-1-(phenylmethyl)propyl]carbamate (H103)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3,4-dichlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H104)	

1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(2,4-dichlorophenyl)ethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H105)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({2-[3,5-bis(methyloxy)phenyl]ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H106)	
1,1-dimethylethyl [(1*S*,2*R*)-3-({2-[2,3-bis(methyloxy)phenyl] ethyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H107)	
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(phenylmethyl)amino]propyl} carbamate (H108)	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(2-phenylethyl)amino]-1-(phenylmethyl)propyl]carbamate (H109)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1-ethylcyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H110)	F110
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-[(1-methylcyclopentyl)amino]-1-(phenylmethyl)propyl]carbamate (H111)	F111
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclopentyl)amino]propyl} carbamate (H112)	F112
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclohexyl)amino]propyl} carbamate (H113)	F113
1,1-dimethylethyl [(1*S*,2*R*)-3-{[2-(3-chlorophenyl)-1,1-dimethylethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H114)	F114

The following BOC-protected amines H115-H147 were prepared in an analogous manner to that described for BOC-protected amine H1, using the appropriate epoxide and the appropriate amine indicated in the table below (only non commercial amines are given):

Boc-protected amine	Epoxide	Amine
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(3-pyridinylmethyl)propyl]carbamate (H115)	K13	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H116)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-3-(cyclohexylamino)-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H117)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]carbamate (H118)	K11	
1,1-dimethylethyl [(1*S*,2*R*)-1-(2-furanylmethyl)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino) propyl]carbamate (H119)	K9	
1,1-dimethylethyl [(1*S*,2*R*)-3-(cyclohexylamino)-1-(2-furanylmethyl)-2-hydroxypropyl]carbamate (H120)	K9	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-1-(2-furanylmethyl)-2-hydroxypropyl]carbamate (H121)	K9	
1,1-dimethylethyl {(1*S*,2*R*)-1-(2-furanylmethyl)-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino]propyl} carbamate (H122)	K9	F5
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl]	K10	

methyl}amino)-1-(2-pyridinylmethyl)propyl]carbamate (H123)		
1,1-dimethylethyl [(1*S*,2*R*)-1-[(4-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H124)	K6	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(4-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H125)	K6	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]carbamate (H126)	K1	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H127)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H128)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-3-(cyclohexylamino)-1-[(3,5-difluorophenyl)methyl]-2-hydroxypropyl}carbamate (H129)	K1	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino]propyl} carbamate (H130)	K1	F5
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H131)	K3	
1,1-dimethylethyl {(1*S*,2*R*)-3-(cyclohexylamino)-1-[(3,4-difluorophenyl)methyl]-2-hydroxypropyl}carbamate (H132)	K3	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}carbamate (H133)	K3	F5
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H134)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H135)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)propyl]carbamate (H136)	K4	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]carbamate (H137)	K4	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(2-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H138)	K4	
1,1-dimethylethyl {(1*S*,2*R*)-1-[(3-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}carbamate (H139)	K5	
1,1-dimethylethyl [(1*S*,2*R*)-1-[(3-fluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)propyl]carbamate (H140)	K2	
1,1-dimethylethyl {(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-1-[(3-fluorophenyl)methyl]-2-hydroxypropyl}carbamate (H141)	K2	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(2-thienylmethyl)propyl]carbamate (H142)	K7	

1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(2-thienylmethyl)propyl]carbamate (H143)	K7	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(1*H*-pyrazol-1-ylmethyl)propyl]carbamate (H144)	K12	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1*H*-pyrazol-1-ylmethyl)propyl]carbamate (H145)	K12	
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(3-thienylmethyl)propyl]carbamate (H146)	K8	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(3-thienylmethyl)propyl]carbamate (H147)	K8	

BOC-protected amines H148-H156 were prepared in an analogous manner to that described for BOC-protected amine H1, substituting cyclohexylamine with the amines indicated in the table below (if amines are not commercially available):

BOC-protected amine	Precursor
1,1-dimethylethyl {(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclobutyl)amino]propyl} carbamate (H148)	F148
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-3-{[1-(1-methylethyl)cyclobutyl]amino}-1-(phenylmethyl)propyl]carbamate (H149)	F149
1,1-dimethylethyl [(1*S*,2*R*)-3-({1-[(3-chlorophenyl) methyl]cyclobutyl} amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H150)	F150
1,1-dimethylethyl [(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)propyl]carbamate (H151)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(1*r*,4*R*)-bicyclo[2.2.1]hept-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H152)	
1,1-dimethylethyl [(1*S*,2*R*)-3-(bicyclo[2.2.2]oct-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H153)	
1,1-dimethylethyl [(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H154)	
1,1-dimethylethyl [(1*S*,2*R*)-3-[(4,4-difluorocyclohexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] carbamate (H155)	F155
1,1-dimethylethyl [(1*S*,2*R*)-3-({[3,4-bis(methyloxy)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H156)	

BOC-protected amine H157

1,1-Dimethylethyl [(1*S*,2*R*)-3-{[(3-ethyl-5-isoxazolyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H157)

1,1-dimethylethyl [(1*S*,2*R*)-3-[[(3-ethyl-5-isoxazolyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]carbamate (H157) was prepared from Description F157 in an analogous manner to the process described for BOC-protected amine H1.

Preparation of Acids

Acid 1

3-Methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1)

To a solution of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B1) (115 mg, 0.433 mmol, 1 equiv) in MeOH (8 ml) was added 2N aqueous NaOH solution (0.65 ml, 1.3 mmol, 3 equiv). The resulting mixture was stirred for 4 h, 2N aqueous NaOH solution (1 ml, mmol, equiv) was added and the resulting solution was stirred for 16 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1) (109 mg, 100%) as a white solid. $[M+H]^+$ = 252.0, RT = 2.61 min

Acid 2

3-Ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2)

Acid 2 was prepared from 125 mg (0.426 mmol) of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B2) in an analogous manner to that described for Acid 1 which yielded 11 mg (98%) of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2) as a white solid. $[M+H]^+$ = 266.1, RT = 2.82 min

Acid 3

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid methyl ester (B3) (144 mg, 0.48 mmol, 1 equiv) in MeOH (10 ml) was added 2N aqueous NaOH solution (2.4 ml, 4.8 mmol, 10 equiv). The resulting mixture was stirred at room temperature for 3.5 h and at 40°C for 1 h, then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3) (136 mg, 100%) as a white solid. $[M+H]^+$ = 288.0, RT = 2.63 min

Acid 4

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4)

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid ethyl ester (B4) (145 mg, 0.44 mmol, 1 equiv) in MeOH (5 ml) was added 2N aqueous NaOH solution (2.2 ml, 4.4 mmol, 10 equiv). The resulting mixture was stirred at room temperature for 3 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 2N aqueous HCl solution and the white precipitate formed extracted twice with AcOEt. The combined organic solutions were dried over Na_2SO_4 and concentrated *in vacuo* to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4) (133 mg, 100%) as a white solid. $[M+H]^+$ = 302.0, RT = 2.83 min

Acid 5

3-Methanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A5)

To a solution of 3-methylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A1) (59 mg, 0.235 mmol, 1 equiv) in MeOH/H_2O (3:1, 24 ml) was added oxone (578 mg, 0.94 mol, 4 equiv). The resulting mixture was stirred at room temperature for 50 min and then concentrated *in vacuo*. The residue was partitioned between AcOEt and H_2O and the layers separated. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a solid which was triturated with Et_2O to give 3-methanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A5) (57 mg, 86%) as a white solid. $[M+H]^+$ = 284.0, RT = 2.05 min

Acid 6

3-Ethanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A6)

Acid 6 was prepared from 59 mg (0.22 mmol) of 3-ethylsulfanyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A2) in an analogous manner to that described for Acid 5 which yielded 59 mg (89%) of 3-ethanesulfonyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A6) as a white solid. $[M+H]^+$ = 298.0, Rt = 2.08 min

Acid 7

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyl-benzoic acid (A7)

Acid 7 was prepared from 78 mg (0.27 mmol) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanyl-benzoic acid (A3) in an analogous manner to that described for Acid 6 which yielded 78 mg (90%) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyl-benzoic acid (A7) as a white solid. $[M-H]^-$ = 318.0, RT = 2.07 min

Acid 8

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonyl-benzoic acid (A8)

Acid 8 was prepared from 72 mg (0.24 mmol) of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanyl-benzoic acid (A4) 73 mg (91%) in an analogous manner to that described in Acid 7 which yielded 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonyl-benzoic acid A8 as a white solid. $[M-H]^-$ = 332.0, RT = 2.14 min

Acids A9-A15 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A9)	A113	B9
3-Propoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A10)	A113	B10
3-Ethoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A11)	A113	B11
3-Isopropoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A12)	A113	B12
3-Pentoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A13)	A113	B13
3-(2-Methoxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A14)	A113	B14
3-(3-Hydroxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A15)	A113	B15

Acid 16

3-(2-Hydroxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A16)

Acid 16 was prepared in accordance with an analogous procedure to that described for Ester 15 from 3-(2-benzyloxy-ethoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (D40).

Acids A17-A22 and A24-A27 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(3-Methoxy-propoxy)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A17)	A113	B17
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy- benzoic acid (A18)	A113	B18
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxy-benzoic acid (A19)	A113	B19
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxy-benzoic acid (A20)	A113	B20
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxy-benzoic acid (A21)	A113	B21
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pentoxy-benzoic acid (A22)	A113	B22
3,5-Bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A24)	A113	B24
4-Chloro-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A25)	A113	B25
4-Methoxy-3,5-bis-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A26)	A113	B26
3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27)	A113	B27

Acid 27 (Alternative Procedure)

3-Nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27)

A flask was charged under nitrogen with 3-bromo-5-nitro-benzoic acid (D5) (12.3 g, 50 mmol, 1 equiv), Cs_2CO_3 (24.4 g, 75 mmol, 1.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (229 mg, 0.25 mmol, 0.005 equiv), Xantphos (433 mg, 0.75 mmol, 0.015 equiv) and dioxan (120 ml). 2-Pyrrolidin-2-one (5.7 ml, 75 mmol, 1.5 equiv) was then added *via syringe* and the resulting mixture was stirred at reflux for 60 h then cooled to room temperature and concentrated *in vacuo*. The residue was diluted with H_2O and 1N aqueous NaOH solution and extracted twice with Et_2O. The aqueous phase was then acidified to pH 1 and extracted three times with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A27) (9.3 g, 75%) as a pale brown solid.

Acids A28-A74 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(2-Oxo-pyrrolidin-1-yl)-5-piperidin-1-yl-benzoic acid (A28)	A113	B28
3-Morpholin-4-yl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A29)	A113	B29
3-(2-Oxo-pyrrolidin-1-yl)-5-phenylamino-benzoic acid (A30)	A113	B30
3-Ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A31)	A114	B31
3-Methylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A32)	A114	B32
3-Diethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A33)	A113	B33
3-Dimethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A34)	A113	B34
3-(2-Oxo-pyrrolidin-1-yl)-5-propylamino-benzoic acid (A35)	A113	B35

3-Isobutylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A36)	A113	B36
3-Benzylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A37)	A113	B37
3-(3-Methyl-butylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A38)	A113	B38
3- Pentylamino-5- (2-oxo-pyrrolidin-1-yl) - benzoic acid (A39)	A113	B39
3- Butylamino-5- (2-oxo-pyrrolidin-1-yl) - benzoic acid (A40)	A113	B40
3-(2,2-Dimethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A41)	A113	B41
3-(Cyclopropylmethyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A42)	A113	B42
3-(1-Ethyl-propylamino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A43)	A113	B43
3-Isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A44)	A113	B44
3-Cyclopentylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A45)	A113	B45
3-Cyclohexylamino-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A46)	A113	B46
3-(Acetyl-methyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A47)	A113	B47
3-(Acetyl-propyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A48)	A114	B48
3-(Acetyl-isopropyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A49)	A114	B49
3-Acetylamino-5-(2-oxo-pyrrolidin- 1-yl)-benzoic acid (A50)	A113	B50
3-(Methanesulfonyl-methyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A51)	A113	B51
3-(Methanesulfonyl-propyl-amino)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A52)	A114	B52
3-Methanesulfonylamino-5-(2-oxo-pyrrolidin-1-yl)- benzoic acid (A53)	A113	B53
3-(2-Oxo-piperidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A54)	A114	B54
3-(2-Oxo-piperidin-1-yl)-5-piperidin-1-yl-benzoic acid (A55)	A114	B55
3-Morpholin-4-yl-5-(2-oxo-piperidin-1-yl)-benzoic acid (A56)	A114	B56
3-Methylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A57)	A114	B57
3-Propylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A58)	A113	B58
3-Ethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A59)	A114	B59
3-Diethylamino-5-(2-oxo-piperidin-1-yl)-benzoic acid (A60)	A113	B60
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzoic acid (A61)	A114	B61
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methylamino-benzoic acid (A62)	A114	B62
3-Diethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A63)	A113	B63
3-Benzylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A64)	A113	B64
3-Butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A65)	A113	B65
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methyl-butylamino)-benzoic acid (A66)	A113	B66
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzoic acid (A67)	A113	B67
3-Pentylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A68)	A113	B68
3-Propylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A69)	A113	B69

3-Ethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A70)	A113	B70
3-(Cyclopropylmethyl-amino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A71)	A113	B71
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzoic acid (A72)	A113	B72
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylamino-benzoic acid (A73)	A114	B73
3-tert-Butoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A74)	A113	B74

Acids A75-A85 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Methoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A75)	A114	B74
3-Hydroxymethyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A76)	A113	B76
5-(2-Oxo-pyrrolidin-1-yl)-*N*-propyl-isophthalamic acid (A77)	A113	B77
N,N-Dimethyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid (A78)	A113	B78
N-Methyl-5-(2-oxo-pyrrolidin-1-yl)-isophthalamic acid (A79)	A113	B79
5-(2-Oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid (A80)	A113	B80
5-(2-Oxo-piperidin-1-yl)-*N,N*-dipropyl-isophthalamic acid (A81)	A113	B81
3-Nitro-5-(2-oxo-piperidin-1-yl)-benzoic acid (A82)	A113	B82
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethyl-benzoic acid (A83)	A113	B83
3-Dimethylaminomethyl-5-(dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A84)	A113	B84
3-Azidomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A85)	A113	B85

Acid 86

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethyl-benzoic acid (A86)

A suspension of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in MeOH (100 ml) was treated with 2N aqueous NaOH solution (10 ml). The resulting mixture was stirred for 4 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethyl-benzoic acid (A86) (140 mg, 89%) as a white solid.

Acid 87

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (A87)

A suspension of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methanesulfonyloxymethyl-benzoic acid methyl ester (D85) (200 mg, 0.55 mmol, 1 equiv) in EtOH (100 ml) was treated with 2N aqueous NaOH solution (10 ml). The resulting mixture was stirred for 4 h at room temperature and then concentrated *in vacuo*. The residue was dissolved in AcOEt (100 ml) and the resulting solution was washed with 2N aqueous HCl solution (50 ml), dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethyl-benzoic acid (A87) (100 mg, 61%) as a white solid.

Acids A88-95 and A100-A102 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzoic acid (A88)	A113	B88
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-propenyl-benzoic acid (A89)	A113	B89
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-butenyl-benzoic acid (A90)	A113	B90
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methyl-propenyl)-benzoic acid (A91)	A113	B91
5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-isophthalamic acid (A92)	A113	B92
3-Cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzoic acid (A93)	A113	B93
5-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-*N,N*-dipropyl-isophthalamic acid (A94)	A113	B94
5-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-*N,N*-dipropyl-isophthalamic acid (A95)	A113	B95
2-Fluoro-3-(2-oxo-pyrrolidin-1-yl)-5-trifluoromethyl-benzoic acid (A100)	A113	B100
3-(2-Oxo-pyrrolidin-1-yl)- (2-methyl-propenyl)-5-benzoic acid (A101)	A113	B101
3-(2-Oxo-pyrrolidin-1-yl)-5-((E)-styryl)-benzoic acid (A102)	A113	B102

The following compounds were prepared from the corresponding alkene in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116):

Acid	Alkene	$[M+H]^+$	RT (min)
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-phenethyl-benzoic acid methyl ester (A103)	A102	310.0	3.12
3-Isobutyl-5-(2-Oxo-pyrrolidin-1-yl)-benzoic acid (A105)	A101	262.1	2.98

Acids A104, A106-A109 and A111-A112 were prepared from the corresponding ester indicated in the below table using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	Ester
3-Isopropyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A104)	A113	B104
3-(2-Oxo-pyrrolidin-1-yl)-5-propyl-benzoic acid (A106)	A113	B106
3-Cyclopentyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A107)	A113	B107

3-Cyclohexyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A108)	A113	B108
3-Ethynyl-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A109)	A114	B109
3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzoic acid (A111)	A114	B111
3-(1,1-Dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propyl-benzoic acid (A112)	A114	B112

Acid 113

3-(2-Oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A113)

To a solution 3-(2-oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid methyl ester (B113) (85 mg, 0.29 mmol, 1 equiv) in THF (5 ml) was added 1N aqueous NaOH solution (0.60 ml, 0.6 mmol, 2 equiv). The resulting mixture was stirred for 14 h then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified using 2N aqueous HCl solution and the white precipitate formed was extracted twice with AcOEt. The combined organic solutions were dried over $MgSO_4$ and concentrated *in vacuo* to give 3-(2-oxo-pyrrolidin-1-yl)-5-pyrrolidin-1-yl-benzoic acid (A113) (77 mg, 95%) as a white solid. $[M+H]^+$ = 275.0, RT = 2.72 min

Acid 114

3-(1,1-Dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114)

A solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid *tert*-butyl ester (B114) (106 mg, 0.29 mmol, 1 equiv) in DCM/TFA (1/1, 4 ml) was stirred at room temperature for 2 h then concentrated *in vacuo*. Traces of solvent were removed by azeotroping with toluene. The residue was triturated with Et_2O to give 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114) (86 mg, 96%) as a pale brown solid. $[M+H]^+$ = 311.1, RT = 2.75 min

Acid 115

3-(4-Methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A115)

To a solution 3-(4-methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid methyl ester (B115) (296 mg, 0.93 mmol, 1 equiv) in THF (10 ml) was added 1N aqueous NaOH solution (1.8 ml, 1.8 mmol, 2 equiv). The resulting mixture was stirred for 14 h then concentrated *in vacuo*. The residual solid was extracted thoroughly with MeOH and the extracts were concentrated *in vacuo* to give 3-(4-methyl-piperazin-1-yl)-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A115) (390 mg, 138%) as an off white solid. $[M+H]^+$ = 304.0, RT = 1.64 min

Acid 116

3-(2-Oxo-piperidin-1-yl)-5-propyl-benzoic acid (A116):

Acid 116 was prepared from Ester 116 in an analogous manner to the process described for Acid 114.

A117-A136, A138-A154 and A156-A176 were prepared from esters B117-B136, B138-B154 and B156-B176, respectively using a procedure analogous to that described in either A113 or A114 (indicated in the below table).

Acid	Procedure	[M+H]+	RT (min)

3-(1,1-Dioxido-6,7-dihydro-1,2-thiazepin-2(3*H*)-yl)-5-propylbenzoic acid (A117)	A113	308.0 ($[M-H]^-$)	2.66
5-(Ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl) benzoic acid (A118)	A113	267.2	1.62
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzoic acid (A119)	A113	317.2	2.23
2-Fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzoic acid (A120)	A113	266.2	2.71
3-(2-Oxo-5-phenyl-1-piperidinyl)-5-propylbenzoic acid (A121)	A114	338.2	3.37
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzoic acid (A122)	A113	303.1	1.98
3-(1,1-Dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-nitrobenzoic acid (A123)	A113	394.1	3.47
3-Amino-5-(1,1-dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)benzoic acid (A124)	A113	347.2	2.83
3-(1,1-Dioxido-4-phenyltetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)benzoic acid (A125)	A113	375.2	3.17
3-Cyclopentyl-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)benzoic acid (A126)	A113	324.0	0.88
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)amino]benzoic acid (A127)	A113	313.2	2.38
3-[Ethyl(methyl)amino]-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A128)	A114	263.3	2.15
3-(Ethylamino)-4-methyl-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A129)	A113	263.1	2.30
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-methylbenzoic acid (A130)	A113	299.0	2.44
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-methylbenzoic acid (A131)	A113	313.1	2.59
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-4-(methyloxy)benzoic acid (A132)	A113	329.1	2.57
3-(Ethylamino)-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl)benzoic acid (A133)	A113	279.1	2.34
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(ethylamino)-4-(methyloxy)benzoic acid (A134)	A113	315.1	2.45
3-(Diethylamino)-5-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-methylbenzoic acid (A135)	A113	341.1	2.05
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E/Z*)-1-propen-1-yl]benzoic acid (A136)	A113	326.0	2.87
3-(1,1-Dioxido-2-isothiazolidinyl)-5-(2-oxo-1-	A113	325.3	2.10

pyrrolidinyl)benzoic acid (A138)			
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-2-(methyloxy)benzoic acid (A139)	A113	329.2	2.02
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A140)	A113	273.0	2.53
3-Ethyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A141)	A113	273.1	2.68
3-Ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A142)	A113	287.4	2.43
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indole-6-carboxylic acid (A143)	A113	309.3	2.40
7-(1,1-Dioxido-2-isothiazolidinyl)-3-ethyl-1*H*-indole-5-carboxylic acid (A144)	A113	309.0	2.79
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-2,3-dihydro-1*H*-indole-6-carboxylic acid (A145)	A113	325.3	2.69
7-(1,1-Dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1*H*-indole-5-carboxylic acid (A146)	A113		
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-indole-6-carboxylic acid (A147)	A113		
7-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-3-ethyl-1*H*-indole-5-carboxylic acid (A148)	A113	340.4	2.68
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-benzimidazole-6-carboxylic acid (A149)	A113	274.4	1.55
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-benzimidazole-6-carboxylic acid (A150)	A113	310.2	1.98
4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-1*H*-benzimidazole-6-carboxylic acid (A151)	A113	340.4	2.68
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indazole-6-carboxylic acid (A152)	A113	274.2	2.10
4-(1,1-Dioxido-2-isothiazolidinyl)-1-ethyl-1*H*-indazole-6-carboxylic acid (A153)	A113	310.3	2.15
4-(2-Oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A154)	A113		
1-Methyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A156)	A113	259.4	2.20
1-Butyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-indole-6-carboxylic acid (A157)	A113	301.0	2.88
4-(2-Oxo-1-pyrrolidinyl)-1-pentyl-1*H*-indole-6-carboxylic acid (A158)	A113	315.1	3.06
3-Methyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylic acid (A159)	A113	260.0	2.59
3-Methyl-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-	A113	259.1	2.48

carboxylic acid (A160)			
3-(1-Methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A161)	A113	287.1	2.82
1-Methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A162)	A113	301.2	2.84
3-Ethyl-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxylic acid (A163)	A113	274.1	2.81
4-Methyl-8-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-chromene-6-carboxylic acid (A164)	A113		
3-Ethyl-7-(2-oxo-1-piperidinyl)-1*H*-indole-5-carboxylic acid (A165)	A113	287.4	2.56
3-Ethyl-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1*H*-indole-5-carboxylic acid (A166)	A113	349.2	3.21
1-Ethyl-4-(2-oxo-1-pyrrolidinyl)-1*H*-1,2,3-benzotriazole-6-carboxylic acid (A167)	A113	275.2	2.38
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzoic acid (A168)	A113	314.15	0.77
3-Cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzoic acid (A169)	A113	310.0	0.83
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethyloxy)benzoic acid (A170)	A113	300.12	0.73
4-Ethyl-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic acid (A171)	A113	290.5	2.00
8-(1,1-Dioxido-2-isothiazolidinyl)-4-ethyl-1,2,3,4-tetrahydro-6-quinoxalinecarboxylic acid (A172)	A113	326.2	2.00
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-propylbenzoic acid (A173)	A113	316.1	2.49
3-(1,1-Dioxido-2-isothiazolidinyl)-2-fluoro-5-propylbenzoic acid (A174)	A113	302.1	2.48
3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-5-[(1-methylethyl)amino]benzoic acid (A175)	A113	316.2	2.30
5-Cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluorobenzoic acid (A176)	A113	342.2	2.89

Acid 137

3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-propylbenzoic acid (A137)

3-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-propylbenzoic acid (A137) was prepared from 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-4-(methyloxy)-5-[(1*E*)-1-propen-1-yl]benzoic acid (A136) in an analogous manner to the process described for 3-(2-oxo-piperidin-1-yl)-5-propyl-benzoic acid *tert*-butyl ester (B116).

Acid 155

4-(1,1-Dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155)

To a solution of methyl 4-amino-1*H*-indole-6-carboxylate (D201) (1.0 g, 5.3 mmol, 1 equiv) in CH_2Cl_2 (50 ml) were added pyridine (0.55 g, 6.5 mmol, 1.2 equiv), 4-chloro-1-butanesulfonyl chloride (1.14 g, 6 mmol, 1.1 equiv) and DMAP (300 mg, 2.45 mmol, 0.5 equiv) and the resulting mixture was stirred at room temperature for 5h. NEt_3 (1 ml, 7.2 mmol, 1.3 equiv) was added and the resulting solution stirred for 2 h then diluted with AcOEt, washed with a 2N aqueous solution, a saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (20 ml) and treated with a 2N aqueous NaOH solution (10 ml, 20 mmol, excess). The resulting solution was stirred at room temperature for 15 h then most of the MeOH was removed *in vacuo*. The residue was partitioned between AcOEt and a 2N aqueous HCl solution. The two layers were separated and the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2/MeOH: 9/1) gave 4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1*H*-indole-6-carboxylic acid (A155) (320 mg, 20%) as a pale pink solid. $[M+H]^+$ = 295.0, RT = 1.90 min.

Preparation of Amines

Amine 1 (C1)

(2R,3S)-3-Amino-1-cyclohexylamino-4-phenyl-butan-2-ol *di*-hydrogen chloride (C1)

((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxy-propyl)-carbamic acid *tert*-butyl ester (BOC-protected amine 1 (H1)) (9 g, 25 mmol, 1 equiv) was dissolved in MeOH (70 ml) and then a 4M solution of HCl in dioxane (60 ml, excess) was added. The resulting mixture was stirred for 3 h at room temperature and then the solvents were removed by evaporation *in vacuo*. The resulting residue was washed with AcOEt and then with Et_2O before drying *in vacuo* to give the title compound (C1) as a white solid (7.4g, 88%).

$[M+H]^+$ 335.31.

Amines C2-C20, C24-C33 and C36 were prepared from their corresponding BOC-protected amines (H2-H20, H24-H33 and H36, respectively) in an analogous manner to that described in C1.

For amines C8-C19, C25-C26 and C29-C32, the 4M HCl in dioxane was replaced with 3 equivalents of p-toluene sulphonic acid to yield the tosic acid salts.

Amine	$[M+H]^+$	RT (min)
(2R,3S)-3-Amino-1-cyclobutylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C2)	235.1	0.32
(2R,3S)-3-Amino-1-isobutylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C3)	237.1	0.86
(2R,3S)-3-Amino-4-phenyl-1-propylamino-butan-2-ol *di*-hydrochloride (C4)	223.1	0.43
(2R,3S)-3-Amino-4-phenyl-1-(1,1,5-trimethyl-hexylamino)-butan-2-ol *di*-hydrochloride (C5)	307.2	2.22
(S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-*N*-cyclohexyl-propionamide *di*-hydrochloride (C6)	F899	-
(2R,3S)-3-Amino-1-[(R)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-	-	-

butan-2-ol *di*-hydrochloride (C7)		
(2R,3S)-3-Amino-1-(1-methyl-1-phenyl-ethylamino)-4-phenyl-butan-2-ol *di*-tosylate (C8)	-	-
(2R,3S)-3-Amino-1-(3-methyl-butylamino)-4-phenyl-butan-2-ol *di*-tosylate (C9)	-	-
(2R,3S)-3-Amino-1-*tert*-butylamino-4-phenyl-butan-2-ol *di*-tosylate (C10)	-	-
(2R,3S)-3-Amino-4-phenyl-1-(3-trifluoromethoxy-benzylamino)-butan-2-ol *di*-tosylate (C11)	-	-
(2R,3S)-3-Amino-1-(2,2,3,3,3-pentafluoro-propylamino)-4-phenyl-butan-2-ol *di*-tosylate (C12)	-	-
(2R,3S)-3-Amino-1-(2,2,3,3,4,4,4-heptafluoro-butylamino)-4-phenyl-butan-2-ol *di*-tosylate (C13)	362	2.9
(2R,3S)-3-Amino-1-(3-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C14)	-	-
(2R,3S)-3-Amino-1-[1-(3-methoxy-phenyl)-1-methyl-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C15)	329.1	2.05
(2R,3S)-3-Amino-4-phenyl-1-[3-(2,2,2-trifluoro-ethyl)-benzylamino]-butan-2-ol *di*-tosylate (C16)	-	-
(2R,3S)-3-Amino-1-[(S)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C17)	-	-
(2R,3S)-3-Amino-1-[(S)-1-(3-methoxy-phenyl)-ethylamino]-4-phenyl-butan-2-ol *di*-tosylate (C18)	-	-
(2R,3S)-3-Amino-1-(5-methyl-hexylamino)-4-phenyl-butan-2-ol *di*-tosylate (C19)	-	-
(2R,3S)-3-Amino-1-(1,5-dimethyl-hexylamino)-4-phenyl-butan-2-ol *di*-hydrochloride (C20)	293.1	2.04
(2R,3S)-3-Amino-1-ethylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C24)	-	-
(2R,3S)-3-Amino-1-(bis-trifluoromethyl-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C25)	-	-
(2R,3S)-3-Amino-1-cyclopropylamino-4-phenyl-butan-2-ol *di*-tosylate (C26)	-	-
(2R,3S)-3-Amino-1-(4-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-hydrochloride (C27)	-	-
(2R,3S)-3-Amino-1-isopropylamino-4-phenyl-butan-2-ol *di*-hydrochloride (C28)	-	-
(2R,3S)-3-Amino-1-(2-methoxy-benzylamino)-4-phenyl-butan-2-ol *di*-tosylate (C29)	301.1	1.7
(2R,3S)-3-Amino-4-phenyl-1-((S)-1-phenyl-ethylamino)-butan-2-ol *di*-tosylate (C30)	-	-
(2R,3S)-3-Amino-4-phenyl-1-((R)-1-phenyl-ethylamino)-butan-2-ol *di*-tosylate (C31)	-	-

(2R,3S)-3-Amino-1-(4-methyl-pentylamino)-4-phenyl-butan-2-ol *di*-tosylate (C32)	-	-
(R)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-3-hydroxy-hexanoic acid isobutyl-amide *di*-hydrochloride (C33)	-	-
(S)-2-((2R,3S)-3-Amino-2-hydroxy-4-phenyl-butylamino)-hexanoic acid isobutyl-amide *di*-hydrochloride (C36)	-	-

Amines C40-C114 were prepared from their corresponding BOC-protected amines H40-H114, respectively) in an analogous manner to that described in C1.

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-1-({1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl} amino)-4-phenyl-2-butanol *di*-tosylate (C40)	367.2	2.44
(2*R*,3*S*)-3-amino-1-({1-[3-(methyloxy)phenyl]cyclohexyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C41)		
(2*R*,3*S*)-3-amino-1-{[(1-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-phenyl-2-butanol *di*-tosylate (C42)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-pyran-4-ylamino)-2-butanol *di*-tosylate (C43)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-tosylate (C44)	265.3	1.52
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1,1,3,3-tetramethylbutyl)amino]-2-butanol *di*-tosylate (C45)	293.3	1.76
(2*R*,3*S*)-3-amino-1-[(1,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-tosylate (C46)	265.3	1.53
(2*R*,3*S*)-3-amino-1-({[4-fluoro-3-(trifluoromethyl)phenyl]methyl} amino)-4-phenyl-2-butanol *di*-tosylate (C47)	357.3	1.79
(2*R*,3*S*)-3-amino-1-[(1,1-dimethylhexyl)amino]-4-phenyl-2-butanol *di*-tosylate (C48)	293.2	2.06
(2*R*,3*S*)-3-amino-1-({[2-methyl-5-(trifluoromethyl)phenyl]methyl} amino)-4-phenyl-2-butanol *di*-tosylate (C49)	353.1	2.09
(2*R*,3*S*)-3-amino-1-[(1*S*)-2,3-dihydro-1*H*-inden-1-ylamino]-4-phenyl-2-butanol *di*-tosylate (C50)		
(1*S*,2*R*)-1-{[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]amino}-2,3-dihydro-1*H*-inden-2-ol *di*-tosylate (C51)	313.1	1.83
(2*R*,3*S*)-3-amino-1-{[6-(methyloxy)-2,3-dihydro-1*H*-inden-1-yl]amino}-4-phenyl-2-butanol *di*-tosylate (C52)	327.5	1.82
(1*R*,2*S*)-1-{[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]amino}-2,3-dihydro-1*H*-inden-2-ol *di*-tosylate (C53)	313.4	1.56
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methylpropyl)thio]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C54)		
(2*R*,3*S*)-3-amino-1-{[1,1-dimethyl-2-(phenyloxy)ethyl]amino}-4-phenyl-2-butanol *di*-tosylate (C55)		
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(phenylmethyl)oxy]ethyl}amino)-	343.5	1.92

4-phenyl-2-butanol *di*-tosylate (C56)		
(2*R*,3*S*)-3-amino-1-{[3-(methyloxy)phenyl]amino}-4-phenyl-2-butanol *di*-tosylate (C57)	287.4	2.11
(2*R*,3*S*)-3-amino-4-phenyl-1-({2-[3-(trifluoromethyl)phenyl]ethyl}amino)-2-butanol *di*-tosylate (C58)	353.4	2.00
(2*R*,3*S*)-3-amino-1-[(1,1-dimethyl-2-phenylethyl)amino]-4-phenyl-2-butanol *di*-tosylate (C59)	313.5	1.98
(2*R*,3*S*)-3-amino-1-{[2-(1-naphthalenyl)ethyl]amino}-4-phenyl-2-butanol *di*-tosylate (C60)	335.4	2.04
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[3-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C61)	343.3	1.93
(2*R*,3*S*)-3-amino-4-phenyl-1-(phenylamino)-2-butanol *di*-tosylate (C62)	257.4	2.06
(2*R*,3*S*)-3-amino-1-({1-[3-(methyloxy)phenyl]cyclopropyl}amino)-4-phenyl-2-butanol *di*-tosylate (C63)	327.5	1.90
(2*R*,3*S*)-3-amino-1-[(cyclohexylmethyl)amino]-4-phenyl-2-butanol *di*-tosylate (C64)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]-2-butanol *di*-tosylate (C65)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tetrahydro-2*H*-thiopyran-4-ylamino)-2-butanol (C66)		
(2*R*,3*S*)-3-amino-1-[(1-methylpropyl)amino]-4-phenyl-2-butanol *di*-tosylate (C67)	-	
(2*R*,3*S*)-3-amino-1-{[4-(1,1-dimethylethyl)cyclohexyl]amino}-4-phenyl-2-butanol *di*-tosylate (C68)	-	
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclobutyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C69)	-	
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methylpropyl)oxy]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C70)	-	
(2*R*,3*S*)-3-amino-1-({1,1-dimethyl-2-[(2-methyl-2-propen-1-yl)oxy]ethyl}amino)-4-phenyl-2-butanol *di*-tosylate (C71)		
(2*R*,3*S*)-3-amino-1-[(1*R*)-2,3-dihydro-1*H*-inden-1-ylamino]-4-phenyl-2-butanol *di*-tosylate (C72)	577.2	2.67
(2*R*,3*S*)-3-amino-1-{[1-(4-methylpentyl)cyclopropyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C73)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclopropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C74)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclopropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C75)		
(2*R*,3*S*)-3-amino-1-(butylamino)-4-phenyl-2-butanol *di*-hydrochloride (C76)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclopropyl)amino]-2-butanol *di*-hydrochloride (C77)		

(2*R*,3*S*)-3-amino-1-{[1-(3-methylbutyl)cyclopropyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C78)		
(2*R*,3*S*)-3-amino-1-{[1-(2-methylpropyl)cyclopropyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C79)		
(2*R*,3*S*)-3-amino-1-({1-[(3-chlorophenyl)methyl]cyclopropyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C80)		
(2*R*,3*S*)-3-amino-1-[(1-methylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C81)		
(2*R*,3*S*)-3-amino-1-[(2*S*)-bicyclo[2.2.1]hept-2-ylamino]-4-phenyl-2-butanol *di*-hydrochloride (C82)		
(2*R*,3*S*)-3-amino-1-[(4,4-dimethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C83)		
(2*R*,3*S*)-3-amino-4-phenyl-1-{[(1*R*)-1,2,2-trimethylpropyl]amino}-2-butanol *di*-hydrochloride (C84)		
(2*R*,3*S*)-3-amino-4-phenyl-1-{[(1*S*)-1,2,2-trimethylpropyl]amino}-2-butanol *di*-hydrochloride (C85)		
(2*R*,3*S*)-3-amino-1-[(2,2-dimethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C86)		
(2*R*,3*S*)-3-amino-1-(pentylamino)-4-phenyl-2-butanol (C87)		
(2*R*,3*S*)-3-amino-1-(hexylamino)-4-phenyl-2-butanol *di*-hydrochloride (C88)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylbutyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C89)		
(2*R*,3*S*)-3-amino-1-[(1,1-dimethylpropyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C90)		
(2*R*,3*S*)-3-amino-1-[(cyclopropylmethyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C91)		
(2*R*,3*S*)-3-amino-1-[(3,3-dimethylcyclopentyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C92)		
(2*R*,3*S*)-3-amino-1-(methylamino)-4-phenyl-2-butanol *di*-hydrochloride (C93)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tricyclo[3.3.1.1^{3,7}]dec-1-ylamino)-2-butanol *di*-hydrochloride (C94)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(1,2,3,4-tetrahydro-1-naphthalenylamino)-2-butanol *di*-hydrochloride (C95)		
(2*R*,3*S*)-3-amino-1-({2-[3-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C96)		
(2*R*,3*S*)-3-amino-1-({2-[4-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C97)		
(2*R*,3*S*)-3-amino-1-({2-[2-(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C98)		
(2*R*,3*S*)-3-amino-1-{[2-(2-chlorophenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C99)		

(2*R*,3*S*)-3-amino-1-{[2-(3-chlorophenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C100)		
(2*R*,3*S*)-3-amino-1-{[2-(4-chlorophenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C101)		
(2*R*,3*S*)-3-amino-1-{[2-(4-methylphenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C102)		
(2*R*,3*S*)-3-amino-1-{[2-(2-methylphenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C103)		
(2*R*,3*S*)-3-amino-1-{[2-(3,4-dichlorophenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C104)		
(2*R*,3*S*)-3-amino-1-{[2-(2,4-dichlorophenyl)ethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C105)		
(2*R*,3*S*)-3-amino-1-({2-[3,5-bis(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C106)		
(2*R*,3*S*)-3-amino-1-({2-[2,3-bis(methyloxy)phenyl]ethyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C107)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(phenylmethyl)amino]-2-butanol *di*-hydrochloride (C108)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(2-phenylethyl)amino]-2-butanol *di*-hydrochloride (C109)		
(2*R*,3*S*)-3-amino-1-[(1-ethylcyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C110)		
(2*R*,3*S*)-3-amino-1-[(1-methylcyclopentyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C111)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclopentyl)amino]-2-butanol *di*-hydrochloride (C112)		
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclohexyl)amino]-2-butanol *di*-hydrochloride (C113)		
(2*R*,3*S*)-3-amino-1-{[2-(3-chlorophenyl)-1,1-dimethylethyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C114)		

Amines C115-C147 were prepared from their corresponding BOC-protected amines H115-H147, respectively in an analogous manner to that described in C1.

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(3-pyridinyl)-2-butanol *tri*-hydrochloride (C115)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C116)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C117)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(1,3-thiazol-2-yl)-2-butanol *di*-hydrochloride (C118)		
(2*R*,3*S*)-3-amino-4-(2-furanyl)-1-({[3-		

(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C119)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(2-furanyl)-2-butanol *di*-hydrochloride (C120)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(2-furanyl)-2-butanol *di*-hydrochloride (C121)		
(2*R*,3*S*)-3-amino-4-(2-furanyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C122)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(2-pyridinyl)-2-butanol *tri*-hydrochloride (C123)		
(2*R*,3*S*)-3-amino-4-(4-chlorophenyl)-1-(cyclohexylamino)-2-butanol *di*-hydrochloride (C124)		
(2*R*,3*S*)-3-amino-4-(4-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C125)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-({[3-(trifluoromethyl) phenyl]methyl} amino)-2-butanol *di*-hydrochloride (C126)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C127)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C128)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(3,5-difluorophenyl)-2-butanol *di*-hydrochloride (C129)		
(2*R*,3*S*)-3-amino-4-(3,5-difluorophenyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C130)		
(2*R*,3*S*)-3-amino-4-(3,4-difluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C131)		
(2*R*,3*S*)-3-amino-1-(cyclohexylamino)-4-(3,4-difluorophenyl)-2-butanol *di*-hydrochloride (C132)		
(2*R*,3*S*)-3-amino-4-(3,4-difluorophenyl)-1-[(1,1,5-trimethylhexyl)amino]-2-butanol *di*-hydrochloride (C133)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C134)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-(cyclohexylamino)-2-butanol *di*-hydrochloride (C135)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C136)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-(cyclohexylamino)-2-butanol		

di-hydrochloride (C137)		
(2*R*,3*S*)-3-amino-4-(2-chlorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C138)		
(2*R*,3*S*)-3-amino-4-(3-chlorophenyl)-1-[(1,5-dimethylhexyl)amino]-2-butanol *di*-hydrochloride (C139)		
(2*R*,3*S*)-3-amino-4-(3-fluorophenyl)-1-({[3-(methyloxy)phenyl]methyl}amino)-2-butanol *di*-hydrochloride (C140)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(3-fluorophenyl)-2-butanol *di*-hydrochloride (C141)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(2-thienyl)-2-butanol *di*-hydrochloride (C142)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(2-thienyl)-2-butanol *di*-hydrochloride (C143)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(1*H*-pyrazol-1-yl)-2-butanol *di*-hydrochloride (C144)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(1*H*-pyrazol-1-yl)-2-butanol *di*-hydrochloride (C145)		
(2*R*,3*S*)-3-amino-1-({[3-(methyloxy)phenyl]methyl}amino)-4-(3-thienyl)-2-butanol *di*-hydrochloride (C146)		
(2*R*,3*S*)-3-amino-1-[(1,5-dimethylhexyl)amino]-4-(3-thienyl)-2-butanol *di*-hydrochloride (C147)		

Amines C148-C156 were prepared from their corresponding BOC-protected amines H148-H156, respectively) in an analogous manner to that described in C1

Amine	$[M+H]^+$	RT (min)
(2*R*,3*S*)-3-amino-4-phenyl-1-[(1-propylcyclobutyl)amino]-2-butanol *di*-hydrochloride (C148)		
(2*R*,3*S*)-3-amino-1-{[1-(1-methylethyl)cyclobutyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C149)		
(2*R*,3*S*)-3-amino-1-({1-[(3-chlorophenyl)methyl]cyclobutyl}amino)-4-phenyl-2-butanol *di*-hydrochloride (C150)		
(2*R*,3*S*)-3-amino-4-phenyl-1-(tricyclo[3.3.1.1^{3,7}]dec-2-ylamino)-2-butanol *di*-hydrochloride (C151)		
(2*R*,3*S*)-3-amino-1-[(1*r*,4*R*)-bicyclo[2.2.1]hept-1-ylamino]-4-phenyl-2-butanol *di*-hydrochloride (C152)		
(2*R*,3*S*)-3-amino-1-(bicyclo[2.2.2]oct-1-ylamino)-4-phenyl-2-butanol *di*-hydrochloride (C153)		
(2*R*,3*S*)-3-amino-1-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C154)	289.5	1.13
(2*R*,3*S*)-3-amino-1-[(4,4-difluorocyclohexyl)amino]-4-phenyl-2-butanol *di*-hydrochloride (C155)	299.3	1.65

(2*R*,3*S*)-3-amino-1-({[3,4-bis(methyloxy)phenyl]methyl}amino)-4-phenyl-2-butanol *di*-tosylate (C156)		

Amine 157

(2*R*,3*S*)-3-Amino-1-{[(3-ethyl-5-isoxazolyl)methyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C157)

(2*R*,3*S*)-3-Amino-1-{[(3-ethyl-5-isoxazolyl)methyl]amino}-4-phenyl-2-butanol *di*-hydrochloride (C157) was obtained from BOC-protected amine H157 in an analogous manner to the process described for amine C1.

Examples

Example 1

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E1)

To a solution of 5-(2-oxo-pyrrolidin-1-yl)-*N,N*-dipropyl-isophthalamic acid (A80) (66 mg, 0.2 mmol, 1 equiv) in DMF (5 ml) at room temperature was added EDAC.HCl (46 mg, 0.24 mmol, 1.2 equiv), HOBT (37 mg, 0.24 mmol, 1.2 equiv), 4-ethylmorpholine (153 µ, 1.2 mmol, 6 equiv) and (S)-2-((2R,3S)-3-amino-2-hydroxy-4-phenyl-butylamino)-*N*-cyclohexyl-propionamide *di*-hydrochloride (C6) (82 mg, 0.2 mmol, 1 equiv). The resulting mixture was stirred for 3 h then concentrated *in vacuo*. The residue was diluted in CH_2Cl_2 and the organic phases washed with a saturated $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by preparative LC/MS gave N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E1) (78 mg, 60%) as a white foam.

[M+H]+ = 648.3

RT = 2.70.

Examples 2-62

Examples 2-62 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N',N'-dipropylisophthalamide (E2)	A80	C6	648.3	2.7
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-isophthalamic acid methyl ester (E3)	A75	C6	579.2	2.47

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-isophthalamic acid tert-butyl ester (E4)	A74	C6	621.2	2.74
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-N'-propylisophthalamide (E5)	A77	C6	606.2	2.45
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-N',N'-dimethyl-5-(2-oxopyrrolidin-1-yl)-isophthalamide (E6)	A78	C6	592.2	2.31
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-N'-methyl-5-(2-oxopyrrolidin-1-yl)-isophthalamide (E7)	A79	C6	578.2	2.29
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-hydroxymethyl-5-(2-oxopyrrolidin-1-yl)benzamide (E8)	A76	C6	551.2	2.28
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-((E)-styryl)benzamide (E9)	A102	C14	590.2	2.83
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-phenethylbenzamide (E10)	A103	C14	592.2	2.80
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E11)	A107	C14	556.3	2.75
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E12)	A107	C6	589.3	2.78
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclohexyl-5-(2-oxopyrrolidin-1-yl)benzamide (E13)	A108	C6	603.3	2.86
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-cyclohexyl-5-(2-oxopyrrolidin-1-yl)benzamide (E14)	A108	C14	570.3	2.84
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino) propyl]-3-(2-oxopyrrolidin-1-yl)-5-propyl-benzamide (E15)	A108	C14	530.2	2.64

N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E16)	A106	C1	492.2	2.61
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(2-methyl-propenyl)-5-(2-oxopyrrolidin-1-yl)benzamide (E17)	A101	C14	542.3	2.69
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-isobutyl-5-(2-oxopyrrolidin-1-yl)benzamide (E18)	A105	C14	544.3	2.73
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-isopropyl-5-(2-oxopyrrolidin-1-yl)benzamide (E19)	A104	C1	492.3	2.60
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-isobutyl-5-(2-oxopyrrolidin-1-yl)benzamide (E20)	A105	C1	506.3	2.71
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E21)	A107	C16	518.4	2.77
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E22)	A107	C16	594.4	2.97
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E23)	A106	C16	568.3	2.69
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide formate salt (E24)	A106	C20	522.4	2.67
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethynyl-5-(2-oxopyrrolidin-1-yl)benzamide (E25)	A109	C16	550.3	2.47
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylbenzamide (E26)	A106	C6	563.4	2.70
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-2-fluoro-3-(2-oxopyrrolidin-1-yl)-5-trifluoromethyl-benzamide formate salt (E27)	A100	C16	612.0	2.76
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-	A176	C16	662.5	3.00

(phenylmethyl)-3-({[3-trifluoromethyl)phenyl]methyl}amino) propyl]benzamide (1:1) (E28)				
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]benzamide (1:1) (E29)	A176	C15	652.5	2.92
formic acid - 5-cyclopentyl-3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (1:1) (E30)	A176	C154	612.5	2.62
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E31)	A175	C16	651.5	2.78
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E32)	A175	C15	641.5	2.65
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-[(1-methylethyl)amino]benzamide (1:1) (E33)	A175	C154	601.5	2.34
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino]propyl}-5-[(1-methylethyl)amino]benzamide (1:1) (E34)	A175	C5	619.6	2.94
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-5-[(1-methylethyl)amino]benzamide (1:1) (E35)	A175	C43	577.5	2.27
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E36)	A24	C6	604.2	2.02
3-Acetylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino) -2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E37)	A50	C6	578.1	2.38
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methanesulfonylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E38)	A53	C6	614.1	2.42

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E39)	A44	C6	578.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propylaminobenzamide (E40)	A35	C6	578.3	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethyl amino)-2-hydroxypropyl]-3-cyclopentylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E41)	A45	C6	604.2	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethyl amino)-2-hydroxypropyl]-3-diethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E42)	A33	C6	592.2	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-morpholin-4-yl-5-(2-oxopyrrolidin-1-yl)benzamide (E43)	A29	C6	606.2	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(4-methylpiperazin-1-yl)-5-(2-oxopyrrolidin-1-yl)benzamide (E44)	A115	C6	619.2	2.05
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-piperidin-1-ylbenzamide (E45)	A28	C6	604.2	2.64
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pyrrolidin-1-ylbenzamide (E46)	A113	C6	590.2	2.65
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-phenylaminobenzamide (E47)	A30	C6	612.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-4-methoxy-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E48)	A26	C6	634.2	2.36
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-4-chloro-3,5-bis-(2-oxopyrrolidin-1-yl)benzamide (E49)	A25	C6	638.1	2.41
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E50)	A31	C6	564.2	2.48

3-Benzylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino) -2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E51)	A37	C6	626.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-methylbutylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E52)	A38	C6	606.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-cyclohexylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E53)	A46	C6	618.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentylaminobenzamide (E54)	A39	C6	606.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1-ethylpropylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E55)	A43	C6	606.2	2.77
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-butylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E56)	A40	C6	592.2	2.7
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2,2-dimethylpropylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E57)	A41	C6	604.2	2.78
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(cyclopropylmethylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E58)	A42	C6	590.2	2.60
3-(Acetylpropylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E59)	A48	C6	620.2	2.47
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E60)	A44	C20	537.3	2.69
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E61)	A27	C6	566.1	2.56
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopyrrolidin-1-yl)benzamide (E62)	A27	C6	566.1	2.56

Example 63

3-Amino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)benzamide (E63)

A mixture of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-nitro-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E62) (40 mg, 0.07 mmol, 1 equiv), 10% Pd on charcoal (50% wet, 10 mg, 12.5% w/w), NH_4COOH (55 mg, 0.90 mmol, 13 equiv), EtOH (5 ml) and H_2O (2.5 ml) was stirred at 50°C for 2 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-amino-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxypropyl]-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E63) (15mg, 38%) as a pale yellow solid.

$[M+H]^+ = 536.1$

RT = 2.27 min

Examples 64-65

Examples 64-65 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-(Acetylisopropylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxo-pyrrolidin-1-yl)benzamide (E64)	A49	C6	620.2	2.44
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(methanesulfonyl propylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E65)	A52	C6	656.2	2.56

Example 66

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E66)

Example 66 (E66) was prepared in an analogous manner to Example 182 from [(2R,3S)-3-({1-[3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D106).

Examples 67-87

Examples 67-87 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)

N-((1S,2R)-1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E67)	A31	C26	451.2	2.23
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E68)	A31	C14	531.2	2.41
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E69)	A31	C24	493.2	2.39
N-((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E70)	A31	C24	439.2	2.20
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E71)	A31	C27	531.2	2.41
N-((1S,2R)-1-Benzyl-2-hydroxy-3-isopropylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E72)	A31	C28	453.2	2.20
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E73)	A31	C16	569.2	2.54
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2,2,3,3,3-pentafluoro-propylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E74)	A31	C12	543.1	2.92
N-[(1S,2R)-1-Benzyl-3-(2,2,3,3,4,4,4-heptafluorobutylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E75)	A31	C13	593.1	3.13
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(R)-1-phenylethylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E76)	A31	C31	515.2	2.38
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-phenylethylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E77)	A31	C30	515.2	2.38
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E78)	A31	C29	531.2	2.37

N-[(1S,2R)-1-Benzyl-3-(3,5-bis-trifluoromethylbenzyl amino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E79)	A31	C25	637.1	2.74
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(R)-1-(3-methoxyphenyl)-ethylamino]-propyl}-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E80)	A31	C7	545.2	2.41
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(S)-1-(3-methoxyphenyl)-ethylamino]-propyl}-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E81)	A31	C17	545.2	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-isobutylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E82)	A36	C6	592.2	2.66
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-dimethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E83)	A34	C6	564.2	2.47
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methyl-1-phenylethylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E84)	A31	C8	529.3	2.44
N-((1S,2R)-1-Benzyl-3-tert-butylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E85)	A31	C10	467.3	2.25
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E86)	A31	C11	585.3	2.61
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylbutylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E87)	A31	C9	481.3	2.38

Example 88

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-isopropylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E88)

Example 88 was prepared in an analogous manner to Example 182 from [(2R,3S)-3-({1-[3-isopropylamino-5-(2-oxo-pyrrolidin-1-yl)-phenyl]-methanoyl}-amino)-2-hydroxy-4-phenyl-butyl]-carbamic acid benzyl ester (D107).
$[M+H]^+$ = 425.2, RT = 2.20 min

Examples 89-102

Examples 89-102 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E89)	A32	C6	550.3	2.37
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(methanesulfonyl methylamino)-5-(2-oxopyrrolidin-1-yl)-benzamide (E90)	A51	C6	628.2	2.41
3-(Acetylmethylamino)-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopyrrolidin-1-yl)-benzamide (E91)	A47	C6	592.2	2.31
N-((1S,2R)-1-Benzyl-3-cyclopentylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E92)	A31	C18	479.2	2.31
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-methylpentylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E93)	A31	C32	495.3	2.51
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(5-methylhexylamino)-propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E94)	A31	C19	509.3	2.62
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethyl-hexylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E95)	A31	C20	523.3	2.68
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E96)	A31	C7	493.2	2.38
N-(1-Benzyl-3-cyclobutylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E97)	A31	C2	465.4	2.29
N-(1-Benzyl-3-cycloheptylamino-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E98)	A31	C33	507.3	2.52
N-(1-Benzyl-2-hydroxy-3-isobutylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E99)	A31	C3	424.2	2.35

N-[1-Benzyl-2-hydroxy-3-(1,1,5-trimethylhexylamino)propyl]-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E100)	A31	C5	537.3	2.80
N-(1-Benzyl-2-hydroxy-3-propylaminopropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E101)	A31	C4	453.2	2.29
N-{1-Benzyl-2-hydroxy-3-[1-(3-methoxyphenyl)-1-methylethylamino]propyl}-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E102)	A31	C15	559.2	2.59

Examples 103-170

Examples 103-170 were prepared by reductive amination using N-((1S,2R)-3-amino-1-benzyl-2-hydroxypropyl)-3-ethylamino-5-(2-oxopyrrolidin-1-yl)benzamide (E66) in an analogous procedure to that described for E183.

Example	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-(3,4-dichloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E103)		
N-((1S,2R)-1-Benzyl-3-benzylamino-2-hydroxy-propyl)-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E104)		
N-[(1S,2R)-1-Benzyl-3-(4-fluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E105)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-trifluoromethyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E106)		
N-{(1S,2R)-1-Benzyl-3-[(furan-2-ylmethyl)-amino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E107)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(quinolin-4-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E108)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-hydroxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E109)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiophen-2-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E110)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiophen-3-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E111)		
N-[(1S,2R)-1-Benzyl-3-(3-chloro-4-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E112)		

N-[(1S,2R)-1-Benzyl-3-(2,3-dichloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E113)		
N-[(1S,2R)-3-(4-Acetylamino-benzylamino)-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E114)		
N-[(1S,2R)-1-Benzyl-3-(4-cyano-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E115)		
N-((1S,2R)-1-Benzyl-2-hydroxy-3-phenethylamino-propyl)-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E116)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(1*H*-indol-3-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E117)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-phenyl-butylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E118)		
N-{(1S,2R)-3-[(1*H*-Benzoimidazol-5-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E119)		
N-{(1S,2R)-1-Benzyl-3-[(E)-3-(4-fluoro-phenyl)-allylamino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E120)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-isopropoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E121)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((E)-3-*p*-tolyl-allylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E122)		
N-{(1S,2R)-1-Benzyl-3-[(2-ethyl-5-methyl-3*H*-imidazol-4-ylmethyl)-amino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E123)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methyl-3-phenyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E124)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxy-4-nitro-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E125)		
N-[(1S,2R)-1-Benzyl-3-(5-cyano-2-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E126)		
N-{(1S,2R)-1-Benzyl-3-[(cyclohex-3-enylmethyl)-amino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E127)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-phenyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E128)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylsulfanyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E129)		
N-[(1S,2R)-1-Benzyl-3-(3-cyano-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E130)		

N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(5-methyl-thiophen-2-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E131)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-methoxy-5-methyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E132)		
N-{(1S,2R)-3-[(Benzofuran-2-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E133)		
N-[(1S,2R)-1-Benzyl-3-(3-fluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E134)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-*p*-tolyl-ethylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E135)		
N-[(1S,2R)-1-Benzyl-3-(dimethylamino-dimethyl-propylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E136)		
N!-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(1#H!-indol-5-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E137)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(2-methyl-thiazol-4-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E138)		
N-[(1S,2R)-1-Benzyl-3-(2-benzyloxy-ethylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E139)		
N-[(1S,2R)-1-Benzyl-3-(3,4-dimethoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E140)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-nitro-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E141)		
N-[(1S,2R)-1-Benzyl-3-(3-chloro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E142)		
N-[(1S,2R)-1-Benzyl-3-(3-ethoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E143)		
N-{(1S,2R)-1-Benzyl-3-[(5-chloro-thiophen-2-ylmethyl)-amino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E144)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(thiazol-2-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E145)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(pyridin-3-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E146)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(4-hydroxy-3-methoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E147)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-hydroxymethyl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E148)		

N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(4-methoxy-phenyl)-propylamino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E149)		
N-[(1S,2R)-1-Benzyl-3-(4-dimethylaminomethyl-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E150)		
N-[(1S,2R)-1-Benzyl-3-(3,4-difluoro-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E151)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(5-methoxymethyl-furan-2-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E152)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-propoxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E153)		
N-[(1S,2R)-1-Benzyl-3-(4-cyano-3-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E154)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-imidazol-1-yl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E155)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-pyrimidin-5-yl-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E156)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(6-methoxy-pyridin-3-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E157)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(6-methoxy-pyridin-2-ylmethyl)-amino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E158)		
N-[(1S,2R)-1-Benzyl-3-(3-*tert*-butoxymethyl-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E159)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-prop-2-ynyloxy-benzylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E160)		
N-[(1S,2R)-3-(3-Acetylamino-benzylamino)-1-benzyl-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E161)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(3-methoxy-phenyl)-propylamino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E162)		
N-{(1S,2R)-1-Benzyl-3-[3-(4-chloro-phenyl)-propylamino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E163)		
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-#p!-tolyl-propylamino)-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E164)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(2*H*-tetrazol-5-yl)-benzylamino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E165)		
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(1*H*-pyrazol-3-yl)-benzylamino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E166)		

N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[3-(1*H*-imidazol-2-yl)-benzylamino]-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E167)		
N-[(1S,2R)-1-Benzyl-3-(4-fluoro-3-methoxy-benzylamino)-2-hydroxy-propyl]-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E168)		
N-{(1S,2R)-1-Benzyl-3-[2,2-dimethyl-3-(2-oxo-pyrrolidin-1-yl)-propylamino]-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E169)		
N-{(1S,2R)-3-[(Benzothiazol-6-ylmethyl)-amino]-1-benzyl-2-hydroxy-propyl}-3-ethylamino-5-(2-oxo-pyrrolidin-1-yl)-benzamide (E170)		

Examples 171-181

Examples 171-181 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-propoxybenzamide formate salt (E171)	A10	C6	579.4	2.34
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E172)	A9	C6	551.2	2.09
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E173)	A12	C6	579.2	2.68
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-hydroxypropoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E174)	A15	C6	595.2	2.40
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(3-methoxypropoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E175)	A17	C6	609.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-hydroxyethoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E176)	A16	C6	581.1	2.36
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-methoxyethoxy)-5-(2-oxopyrrolidin-1-yl)benzamide (E177)	A14	C6	595.2	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E178)	A13	C6	607.2	2.87
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((S)-1-isobutyl carbamoyl-pentylamino)-propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E179)	A12	C36	595.2	2.75

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E180)	A12	C14	546.1	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E181)	A11	C6	565.2	2.54

Example 182

N-((1S,2R)-3-Amino-1-benzyl-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E182)

A mixture of [(2R,3S)-2-hydroxy-3-({1-[3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-phenyl]-methanoyl}-amino)-4-phenyl-butyl]-carbamic acid benzyl ester (D105) (820 mg, 1.4 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 100 mg, 6% w/w), NH_4CO_2H (800 mg, 12.7 mmol, 9 equiv), EtOH (25 ml) and H_2O (10 ml) was stirred at 60°C for 1 h. The mixture was then cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and H_2O. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give *N*-((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (420 mg, 66%) as a white solid.
$[M+H]^+$ = 454.0, RT = 2.63 min

Example 183

N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-propylbutylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E183)

To a solution of *N*-((1S,2R)-3-amino-1-benzyl-2-hydroxy-propyl)-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (E182) (30 mg, 0.066 mmol, 1equiv) in $(CH_2Cl)_2$ (5 ml) were added sodium triacetoxyborohydride (20 mg, 0.094 mmol, 1.4 equiv), 4-heptanone (10 µl, 0.070 mmol, 1.1 equiv) and CH_3COOH (4 µl, 0.070 mmol, 1,1 equiv). The resulting mixture was stirred at room temperature for 92 hours, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (*iso*-hexane/ethyl acetate : 3/2) gave *N*-[(1S,2R)-1-benzyl-2-hydroxy-3-(1-propyl-butylamino)-propyl]-3-(2-oxo-pyrrolidin-1-yl)-5-pentyloxy-benzamide (4.2 mg, 11%) as a colourless oil. $[M+H]^+$ = 552.2, RT = 2.98 min

Examples 184-192

The following compounds were prepared in an analogous manner to Example 183 from 3-pentoxy-5-(2-oxo-pyrrolidin-1-yl)-benzoic acid (A13) and the appropriate aldehyde or ketone:

Example	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5- pentyloxybenzamide (E184)	574.2	2.87
N-((1S,2R)-1-Benzyl-3-benzylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E185)	544.1	2.83

N-((1S,2R)-1-Benzyl-3-ethylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxy-benzamide (E186)	482.2	2.70
N-((1S,2R)-1-Benzyl-2-hydroxy-3-phenethylaminopropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E187)	558.2	2.91
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(2-phenylpropylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E188)	572.2	2.95
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E189)	536.2	2.84
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(1-methylpiperidin-4-ylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E190)	551.2	2.43
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methylbutylamino)-propyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E191)	524.2	2.87
N-[(1S,2R)-1-Benzyl-3-(1-ethylpropylamino)-2-hydroxypropyl]-3-(2-oxopyrrolidin-1-yl)-5-pentyloxybenzamide (E192)	594.3	3.09

Examples 193-204

Examples 193-204 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxy-propyl]-3-isopropoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E193)	A11	C20	538.3	2.81
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E194)	A11	C16	570.3	2.64
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide formate salt (E195)	A11	C20	524.3	2.74
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E196)	A11	C1	494.3	2.45
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-ethoxy-5-(2-oxopyrrolidin-1-yl)benzamide (E197)	A11	C14	532.3	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexyl carbamoylethylamino)-2-hydroxypropyl]-3-methanesulfonyl-5-(2-oxopyrrolidin-1-yl)benzamide (E198)	A5	C6	599.1	2.41

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-methylsulfanyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E199)	A1	C16	572.2	2.72
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethylsulfanyl-5-(2-oxopyrrolidin-1-yl)benzamide (E200)	A2	C16	586.2	2.80
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-ethanesulfonyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E201)	A6	C16	618.2	2.70
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-methanesulfonyl-5-(2-oxopyrrolidin-1-yl)-benzamide (E202)	A5	C16	604.1	2.57
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-N',N'-dipropylisophthalamide (E203)	A94	C6	684.2	2.67
3-Azidomethyl-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E204)	A85	C6	612.2	2.52

Example 205

3-Aminomethyl-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E205)

A mixture of 3-azidomethyl-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (E204) (70 mg, 0.12 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 20 mg, 15% w/w), NH_4COOH (65 mg, 1 mmol, 9 equiv), EtOH (5 ml) and H_2O (2.5 ml) was stirred at 50°C for 2 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give 3-aminomethyl-*N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (20 mg, 30%) as a white solid.

$[M+H]^+ = 586.2$

RT = 1.98 min

Examples 206-207

Examples 206-207 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-dimethylaminomethyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-benzamide (E206)	A84	C6	614.2	1.99
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-vinyl-benzamide (E207)	A88	C6	583.1	2.53

Example 208

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethyl-benzamide (E208)

Example 208 was prepared from Example 214 in an analogous manner to that described for Example 213. $[M+H]^+$ = 585.2, RT = 2.56min

Examples 209-212

Examples 209-212 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxymethylbenzamide (E209)	A86	C6	601.2	2.41
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxymethylbenzamide (E210)	A87	C6	615.2	2.50
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(Z/E)-propenylbenzamide (E211)	A89	C6	597.2	2.61
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(Z/E)-but-1-enyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E212)	A90	C6	611.2	2.70

Example 213

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-

hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E213)

A mixture of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propenyl-benzamide (E211) (50 mg, 0.083 mmol, 1 equiv), 10% palladium on charcoal (50% wet, 15 mg, 15% w/w), NH_4COOH (50 mg, 0.79 mmol, 9 equiv) and EtOH (5 ml) was stirred at 60°C for 1 h, cooled to room temperature and the catalyst was filtered off through a pad of celite. Most of the EtOH was removed *in vacuo* and the residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O to give of *N*-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoyl-ethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propyl-benzamide (45 mg, 90%) as a white solid.
$[M+H]^+$ = 599.2, RT = 2.63min

Example 214

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-butyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E214)

Example 214 was prepared from N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(Z/E)-but-1-enyl-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E212) in an analogous manner to that described in Example 213. $[M+H]^+$ = 613.2, RT = 2.75min

Examples 215-216

Examples 215-216 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(2-methylpropenyl)-benzamide (E215)	A91	C6	611.2	2.70
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-fluoromethylbenzamide (E216)	A83	C6	589.2	2.44

Example 217

N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxy-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isobutylbenzamide (E217)

Example 217 was prepared from Example 215 in an analogous manner to that described in Example 213. $[M+H]^+$ = 613.3, RT = 2.72min

Examples 218-220 and 222

Examples 218-220 and 222 were prepared in an analogous manner to Example 213 from the appropriate amine indicated in the table below:

Example	Amine	$[M+H]^+$	RT (min)
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E218)	C16	604.3	2.76
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide formate salt (E219)	C26	558.3	2.87
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylbenzamide (E220)	C6	528.3	2.61
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propyl-benzamide (E222)	C14	566.2	2.64

Examples 221 and 223-226

Examples 221 and 223-226 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)isophthalamide (E221)	A92	C6	600.2	2.23
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E223)	A93	C6	582.2	2.47
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-cyano-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E224)	A93	C16	587.2	2.43
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzyl amino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethynyl-benzamide formate salt (E225)	A111	C16	586.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-nitro-5-(2-oxopiperidin-1-yl)benzamide (E226)	A82	C6	580.2	2.55

Example 227

3-Amino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-5-(2-oxopiperidin-1-yl)benzamide (E227)

Example 227 was prepared from Example 226 in an analogous manner to the process described for Example 63. $[M+H]^+$ = 550.1, RT = 2.31min

Examples 228-251

Examples 228-251 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-propylaminobenzamide (E228)	A58	C6	592.2	2.59
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-diethylamino-5-(2-oxopiperidin-1-yl)benzamide (E229)	A60	C6	606.3	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-ethylamino-5-(2-oxopiperidin-1-yl)benzamide (E230)	A59	C6	578.2	2.46
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-methylamino-5-(2-oxopiperidin-1-yl)benzamide (E231)	A57	C6	564.3	2.40
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-piperidin-1-ylbenzamide (E232)	A55	C6	618.3	2.65
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-morpholin-4-yl-5-(2-oxopiperidin-1-yl)benzamide (E233)	A56	C6	620.3	2.43
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(2-oxopiperidin-1-yl)-5-pyrrolidin-1-yl-benzamide (E234)	A54	C6	604.3	2.64
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylaminobenzamide (E235)	A72	C6	614.2	2.58
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-((1S,2R)-2-hydroxy-1-isobutylcarbamoyl-pentylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylamino-benzamide (E236)	A72	C33	646.2	2.63

3-Benzylamino-N-[(1S,2R)-1-benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxy-propyl]-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E237)	A64	C6	662.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-butylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E238)	A65	C6	628.2	2.71
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-(3-methylbutylamino)-benzamide (E239)	A66	C6	642.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-phenethylamino-benzamide (E240)	A67	C6	676.2	2.80
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pentylaminobenzamide (E241)	A68	C6	642.2	2.79
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propylaminobenzamide (E242)	A69	C6	614.2	2.57
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E243)	A70	C6	600.2	2.47
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-diethylamino-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E244)	A63	C6	628.2	2.63
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E245)	A70	C20	559.2	2.68
N-[(1S,2R)-1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropylaminobenzamide (E246)	A72	C20	573.2	2.77

N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(cyclopropylmethylamino)-5-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)benzamide (E247)	A71	C6	626.2	2.59
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylamino-benzamide formate salt (E248)	A70	C14	567.2	2.44
N-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide formate salt (E249)	A70	C16	605.1	2.60
N-((1S,2R)-1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylaminobenzamide (E250)	A70	C1	529.3	2.40
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-morpholin-4-yl-benzamide formate salt (E251)	A61	C16	647.3	2.39

Example 252

***N*-[(1S,2R)-1-Benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzamide formate salt (E252)**

To a solution of 3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzoic acid (A114) (62 mg, 0.2 mmol, 1 equiv) in DMF (5 ml) at room temperature was added (2R,3S)-3-amino-4-phenyl-1-(3-trifluoromethyl-benzylamino)-butan-2-ol (C16) (82 mg, 0.2 mmol, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (46 mg, 0.24 mmol, 1.2 equiv), 1-hydroxybenzotriazole hydrate (37 mg, 0.24 mmol, 1.2 equiv) and 4-ethylmorpholine (152 µl, 1.2 mmol, 6 equiv). The resulting mixture was stirred for 4 h then concentrated *in vacuo*. The residue was diluted with AcOEt and the organic phase washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration with Et_2O to yield *N*-[(1S,2R)-1-benzyl-2-hydroxy-3-(3-trifluoromethyl-benzylamino)-propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pyrrolidin-1-yl-benzamide as a white solid (46 mg, 36%). $[M+H]^+$ = 631.2, RT = 2.65 min

Examples 253-289

Examples 253-289 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1-l6-isothiazolidin-2-yl)-5-methylaminobenzamide formate salt (E253)	A62	C16	591.2	2.58
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E254)	A18	C6	601.2	2.54
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxy-benzamide (E255)	A18	C16	606.2	2.66
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide formate salt (E256)	A18	C20	560.3	2.74
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E257)	A18	C14	568.3	2.50
N-(1-Benzyl-3-cyclohexylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E258)	A18	C1	530.2	2.47
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-isopropoxybenzamide (E259)	A19	C6	615.4	2.68
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-propoxybenzamide (E260)	A21	C6	615.4	2.89
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-pentyloxybenzamide (E261)	A22	C6	643.5	2.89
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methoxybenzamide (E262)	A20	C6	587.4	2.49
N-(1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E263)	A18	C26	488.2	2.37
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino) propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethoxybenzamide (E264)	A18	C11	622.2	2.91

N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-methylsulfanylbenzamide (E265)	A3	C16	608.2	2.73
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethylsulfanylbenzamide (E266)	A4	C16	622.2	2.82
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-ethanesulfonylbenzamide (E267)	A8	C16	654.1	2.65
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-3-(1,1-dioxo-1λ^6-isothiazolidin-2-yl)-5-Methanesulfonylbenzamide (E268)	A7	C16	640.2	2.62
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(2-oxopiperidin-1-yl)-N',N'-dipropylisophthalamide (E269)	A81	C6	662.3	2.63
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-2-fluoro-*N*-{(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)amino]benzamide (1:1) (E270)	A175	C11	667.4	2.82
3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-3-{[(3-ethyl-5-isoxazolyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluorobenzamide (E271)	A119	C157	588.4	2.30
4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1*H*-benzimidazole-6-carboxamide (E272)	A151	C43	570.4	1.91
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2*H*-pyran-4-ylamino)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E273)	A172	C43	572.4	2.08
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-3-{[(1-ethyl-1*H*-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E274)	A172	C154	596.4	2.15
4-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-1-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-1*H*-benzimidazole-6-carboxamide (E275)	A151	C28	528.4	1.92
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-*N*-[(1*S*,2*R*)-2-hydroxy-3-[(1-methylethyl)amino]-1-	A172	C28	530.4	2.11

(phenylmethyl)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E276)				
N-[(1S,2R)-1-Benzyl-3-((S)-1-cyclohexylcarbamoyl ethylamino)-2-hydroxypropyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E277)	A95	C6	698.2	2.68
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino)propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E278)	A95	C16	703.3	2.87
N-(1-Benzyl-3-cyclopropylamino-2-hydroxypropyl)-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropylisophthalamide (E279)	A95	C26	585.3	2.55
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide (E280)	A112	C16	618.2	3.07
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide formate salt (E281)	A112	C14	580.3	2.77
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide formate salt (E282)	A112	C20	572.3	3.01
N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-propylbenzamide (E283)	A112	C6	613.4	2.80
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropyl-isophthalamide (E284)	A95	C14	665.3	2.85
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethoxybenzylamino) propyl]-5-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-N',N'-dipropyl-isophthalamide formate salt (E285)	A95	C11	719.2	3.02
N-[1-Benzyl-2-hydroxy-3-(3-trifluoromethylbenzylamino) propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E286)	A73	C16	619.2	2.73
N-[1-Benzyl-2-hydroxy-3-(3-methoxybenzylamino)propyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E287)	A73	C14	581.2	2.72
N-[1-Benzyl-3-(1,5-dimethylhexylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide formate salt (E288)	A73	C20	573.3	2.99

N-[1-Benzyl-3-(1-cyclohexylcarbamoylethylamino)-2-hydroxypropyl]-3-(1,1-dioxo-1λ^6-[1,2]thiazinan-2-yl)-5-ethylaminobenzamide (E289)	A73	C6	614.3	2.75

Examples 290-427 (E290-E427)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E290)	D120	619.3	2.69
formic acid - N-{(1S,2R)-1-Benzyl-3-[(2-fluoro-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E291)	D120	599.4	2.48
formic acid - N-{(1S,2R)-1-Benzyl-3-[(4-fluoro-3-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E292)	D120	599.4	2.52
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,5-dimethylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E293)	D120	579.3	2.68
N-{(1S,2R)-1-Benzyl-3-[(3,5-difluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E294)	D120	587.3	2.61
N-((1S,2R)-1-Benzyl-2-hydroxy-3-{[3-nitro-5-(trifluoromethyl)benzyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E295)	D120	664.2	2.78
N-((1S,2R)-1-Benzyl-3-{[(5-cyanopyridin-3-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E296)	D120	577.3	2.42
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-chloro-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E297)	D120	615.3	2.70
N-{(1S,2R)-1-Benzyl-3-[(3-bromo-5-fluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E298)	D120	649.2	2.70
5-{[((2R,3S)-3-{[3-(1,1-Dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl]amino}-2-hydroxy-4-phenylbutyl)amino]methyl}-N-methylnicotinamide (E299)	D120	609.3	2.34
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-bromo-5-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E300)	D120	661.2	2.71

Methyl 5-{[((2R,3S)-3-{[3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl] amino}-2-hydroxy-4-phenylbutyl)amino]methyl} nicotinate (E301)	D120	610.3	2.44
N-{(1S,2R)-1-Benzyl-3-[(3,5-di-tert-butylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E302)	D120	663.4	3.14
N-((1S,2R)-1-Benzyl-2-hydroxy-3-{[3-methyl-5-(methylsulfonyl)benzyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E303)	D120	643.3	2.53
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-methoxy-5-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E304)	D120	595.3	2.65
Dimethyl 5-{[((2R,3S)-3-{[3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl] amino}-2-hydroxy-4-phenylbutyl)amino]methyl} isophthalate (E305)	D120	667.3	2.63
N-{(1S,2R)-1-Benzyl-3-[(3,5-diisopropoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E306)	D120	667.4	2.91
N-((1S,2R)-1-Benzyl-3-{[(4-bromo-2-thienyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E307)	D120	637.3	2.56
N-{(1S,2R)-1-Benzyl-3-[(2,3-dihydro-1-benzofuran-6-ylmethyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E308)	D120	593.3	2.42
formic acid - N-((1S,2R)-1-Benzyl-3-{[(4-chloro-1-methyl-1H-pyrazol-3-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E309)	D120	589.3	2.26
N-((1S,2R)-1-Benzyl-3-{[(2-bromo-1,3-thiazol-5-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E310)	D120	638.2	2.36
N-((1S,2R)-1-Benzyl-3-{[(4-bromo-1H-pyrrol-2-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E311)	D120	618.2	2.54
formic acid - N-((1S,2R)-1-Benzyl-3-{[(2-butyl-1H-imidazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E312)	D120	597.4	2.11
N-{(1S,2R)-1-Benzyl-3-[(3-bromobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E313)	D120	631.2	2.59
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-nitrobenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E314)	D120	596.3	2.45
N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-thienylmethyl) amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E315)	D120	557.3	2.36
N-((1S,2R)-1-Benzyl-3-{[(4-bromo-1-methyl-1H-pyrazol-3-	D120	635.3	2.33

yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E316)			
N-((1S,2R)-1-Benzyl-3-{[3-fluoro-5-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E317)	D120	637.3	2.68
formic acid - N-{(1S,2R)-1-Benzyl-2-hydroxy-3-[(3-vinylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E318)	D120	577.3	2.43
formic acid - N-((1S,2R)-1-Benzyl-2-hydroxy-3-{[(4-methoxy-3-thienyl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E319)	D120	587.3	2.31
3-{[((2R,3S)-3-{[3-(1,1-Dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzoyl]amino}-2-hydroxy-4-phenylbutyl)amino]methyl}benzoic acid - formic acid (1:1) (E320)	D120	595.3	2.27
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3,4-dimethoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E321)	D120	611.3	2.28
formic acid - N-((1S,2R)-1-Benzyl-3-{[(5-ethyl-2-furyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E322)	D120	567.4	2.34
formic acid - N-{(1S,2R)-1-Benzyl-3-[(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E323)	D120	609.4	2.32
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-ethoxy-4-methoxybenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E324)	D120	625.4	2.36
formic acid - N-((1S,2R)-1-Benzyl-3-{[(5-ethyl-2-thienyl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E325)	D120	585.3	2.46
formic acid - N-{(1S,2R)-1-Benzyl-3-[(3-chloro-4-fluorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E326)	D120	603.3	2.49
formic acid - N-((1S,2R)-1-Benzyl-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E327)	D120	569.4	2.13
formic acid - N-((1S,2R)-1-Benzyl-3-{[(1-ethyl-3-methyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E328)	D120	583.4	2.17
formic acid - N-((1S,2R)-1-Benzyl-3-{[(2,2-dimethyl-3,4-dihydro-2H-chromen-6-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E329)	D120	635.4	2.60
formic acid - N-((1S,2R)-1-Benzyl-3-{[4-chloro-3-(trifluoromethyl)benzyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-	D120	653.3	2.69

1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E330)			
formic acid - N-((1S,2R)-1-Benzyl-2-hydroxy-3-{[(6-methylpyridin-2-yl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E331)	D120	566.3	2.22
formic acid - N-{(1S,2R)-1-benzyl-3-[(3-ethylbenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E332)	D120	579.5	2.40
N-((1S,2R)-1-benzyl-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (E333)	D121	587.4	2.08
formic acid - N-((1S,2R)-1-benzyl-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxypropyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E334)	E66	519.5	2.00
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxy-4-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E335)	D120	595.2	2.65
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxy-2-methylbenzyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E336)	D120	595.4	2.60
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide (E337)	D120	531.5	0.75
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylbutyl)amino]propyl} benzamide hydrochloride (E338)	D120	559.5	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylpentyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E339)	D120	545.5	0.84
N-[(1S,2R)-3-[(1,4-dimethylpentyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E340)	D120	559.5	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E341)	D120	531.5	0.81
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(propylamino)propyl] benzamide hydrochloride E342)	D120	503.5	0.72
N-[(1S,2R)-3-{[1-(3-chlorophenyl)propyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E343)	E66	563.5	0.84
N-[(1S,2R)-3-{[1-(3-chlorophenyl)propyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E344)	D122	588.4	1.01

3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(4-methylpentyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E345)	D120	545.5	0.85
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(5-methylhexyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E346)	D120	559.6	0.89
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylpropyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E347)	D120	517.5	0.74
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylhexyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E348)	D120	559.6	0.89
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E349)	D123	672.3	0.89
N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(phenylmethyl)amino]propyl}-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E350)	D123	516.5	0.78
N-[(1S,2R)-3-{[(3-bromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E351)	D123	596.2	0.83
N-[(1S,2R)-3-({[3-(ethyloxy)phenyl]methyl} amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E352)	D123	560.4	0.82
N-[(1S,2R)-3-{[(3-chlorophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E353)	D123	550.3	0.82
N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E354)	D123	600.3	0.87
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E355)	D123	576.4	0.81
N-[(1S,2R)-3-{[(3,5-dichlorophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E356)	D123	584.2	0.87
N-[(1S,2R)-3-{[(3,5-difluorophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E357)	D123	552.3	0.80
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E358)	D123	584.3	0.85
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-	D123	652.3	0.93

hydroxy-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E359)			
N-[(1S,2R)-2-hydroxy-3-{[(3-methylphenyl)methyl]amino}-1-(phenylmethyl)propyl]-3-[(1-methylethyl)oxy]-5-(2-oxo-1-pyrrolidinyl)benzamide (E360)	D123	530.4	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E361)	D124	634.3	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E362)	D124	596.3	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)oxy]benzamide hydrochloride (E363)	D124	650.3	0.89
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E364)	D124	702.3	0.96
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E365)	D124	626.3	0.82
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E366)	D124	722.1	0.90
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E367)	D125	644.4	0.94
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E368)	D125	606.4	0.88
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E369)	D125	660.4	0.95
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E370)	D125	712.4	1.02

N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E371)	D125	636.4	0.90
3-cyclopentyl-N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E372)	D125	732.2	0.99
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E373)	D120	635.3	0.83
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E374)	D120	687.3	0.89
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E375)	D120	611.4	0.77
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E376)	D120	707.2	0.85
3-(ethyloxy)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E377)	D126	586.2	0.82
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E378)	D126	638.2	0.88
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E379)	D126	562.3	0.75
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E380)	D126	658.0	0.83
3-cyclopentyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E381)	D122	610.3	0.92
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E382)	D122	662.3	0.99
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E383)	D122	586.3	0.86
3-cyclopentyl-N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(2-oxo-1-	D122	682.1	0.94

pyrrolidinyl)benzamide hydrochloride (E384)			
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E385)	E66	561.3	0.73
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E386)	E66	657.1	0.80
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E387)	D127	674.2	0.88
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E388)	D127	598.3	0.76
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)benzamide hydrochloride (E389)	D127	694.1	0.84
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E390)	D128	620.2	0.84
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl]-5-[(1-methylethyl)oxy]benzamide hydrochloride (E391)	D128	582.3	0.77
3-(1,1-dioxido-2-isothiazolidinyl)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl}-5-[(1-methylethyl)oxy]benzamide hydrochloride (E392)	D128	636.2	0.85
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E393)	D128	688.2	0.91
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E394)	D128	612.2	0.80
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-[(1-methylethyl)oxy]benzamide hydrochloride (E395)	D128	708.1	0.87
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E396)	D129	630.2	0.90
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E397)	D129	592.3	0.84
3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)-N-{(1S,2R)-2-	D129	646.3	0.91

hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E398)			
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E399)	D129	698.3	0.98
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E400)	D129	622.3	0.86
3-cyclopentyl-N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(1,1-dioxido-2-isothiazolidinyl)benzamide hydrochloride (E401)	D129	718.1	0.94
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino]propyl}benzamide hydrochloride (E402)	D130	621.3	0.80
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E403)	D130	673.3	0.86
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E404)	D130	597.4	0.73
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)benzamide hydrochloride (E405)	D130	693.2	0.82
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide hydrochloride (E406)	D131	620.3	0.83
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(phenylmethyl)propyl] benzamide hydrochloride (E407)	D131	582.4	0.78
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy]phenyl}methyl)amino]propyl} benzamide hydrochloride (E408)	D131	636.3	0.86
N-[(1S,2R)-3-({[3,5-bis(trifluoromethyl)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide hydrochloride (E409)	D131	688.3	0.93
N-[(1S,2R)-3-({[3,5-bis(methyloxy)phenyl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethyloxy)benzamide hydrochloride (E410)	D131	612.3	0.79
N-[(1S,2R)-3-{[(3,5-dibromophenyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-	D131	708.1	0.88

yl)-5-(ethyloxy)benzamide hydrochloride (E411)			
N-[(1S,2R)-3-{[1-(3-chlorophenyl)propyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E412)	D120	613.3	0.92
3-cyclopentyl-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-[(1-methylbutyl)amino]-1-(phenylmethyl)propyl] benzamide hydrochloride (E413)	D125	556.6	0.92
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-2-ylamino)propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E414)	D122	566.5	0.9
N-[(1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-2-ylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E415)	D122	552.6	0.9
N-[(1S,2R)-1-benzyl-3-(2,3-dihydro-1H-inden-2-ylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E416)	D120	577.5	0.8
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-2-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E417)	D120	591.5	0.8
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)amino]propyl}-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E418)	D122	596.6	0.9
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide (E419)	D122	594.5	2.5
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidoisothiazolidin-2-yl)-5-ethoxybenzamide (E420)	D127	606.4	2.3
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidoisothiazolidin-2-yl)-5-isopropoxybenzamide (E421)	D128	620.4	2.3
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-cyclopentyl-5-(1,1-dioxidoisothiazolidin-2-yl)benzamide (E422)	D129	630.4	2.5
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-ethoxybenzamide (E423)	D131	620.3	2.3
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-isopropoxybenzamide (E424)	D124	634.3	2.4
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (E425)	D125	644.4	2.6

N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E426)	E66	568.8	2.2
N-{(1S,2R)-1-benzyl-3-[(3,5-dichlorobenzyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidoisothiazolidin-2-yl)-5-(ethylamino)benzamide hydrochloride (E427)	D130	604.9	2.2

Examples 428-570 (E428-E570)

Examples E428-E570 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-{[1-(4-methylpentyl)cyclopropyl] amino}-1-(phenylmethyl)propyl] benzamide hydrochloride (E428)	A73	C73	585.6	0.90
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[(1-ethylcyclopropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide hydrochloride (E429)	A73	C74	529.5	0.73
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-{[1-(1-methylethyl)cyclopropyl] amino}-1-(phenylmethyl)propyl] benzamide hydrochloride (E430)	A73	C75	543.4	0.77
N-[(1S,2R)-3-(butylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E431)	A73	C76	517.4	0.75
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propyl cyclopropyl)amino]propyl}benzamide hydrochloride (E432)	A73	C77	543.5	0.79
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-{[1-(3-methylbutyl)cyclopropyl] amino}-1-(phenylmethyl)propyl] benzamide hydrochloride (E433)	A73	C78	571.6	0.88
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-{[1-(2-methylpropyl)cyclopropyl]amino}-1-(phenylmethyl)propyl] benzamide hydrochloride (E434)	A73	C79	557.5	0.84
N-[(1S,2R)-3-({1-[(3-chlorophenyl)methyl] cyclopropyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E435)	A73	C80	625.4	0.90
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1-methylcyclohexyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-	A73	C81	557.5	0.78

2-yl)-5-(ethylamino)benzamide hydrochloride (E436)				
N-{(1S,2R)-1-benzyl-3-[(1S,2S,4R)-bicyclo[2.2.1]hept-2-ylamino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E437)	A73	C82	555.4	0.78
N-{(1S,2R)-1-benzyl-3-[(4,4-dimethylcyclohexyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E438)	A73	C83	571.3	0.82
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1R)-1,2,2-trimethylpropyl]amino} propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E439)	A73	C84	545.6	0.8
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1S)-1,2,2-trimethylpropyl]amino} propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E440)	A73	C85	545.6	0.81
N-{(1S,2R)-1-benzyl-3-[(2,2-dimethylcyclohexyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E441)	A73	C86	571.6	0.83
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(pentylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E442)	A73	C87	531.5	0.84
N-[(1S,2R)-1-benzyl-3-(hexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E443)	A73	C88	545.5	0.9
N-{(1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E444)	A73	C89	545.5	0.86
N-{(1S,2R)-1-benzyl-3-[(1,1-dimethylpropyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E445)	A73	C90	531.5	0.8
N-{(1S,2R)-1-benzyl-3-[(cyclopropylmethyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E446)	A73	C91	515.5	0.76
N-{(1S,2R)-1-benzyl-3-[(3,3-dimethylcyclopentyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E447)	A73	C92	557.6	0.81
N-[(1S,2R)-1-benzyl-3-(ethylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E448)	A73	C24	489.5	0.7
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(methylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E449)	A73	C93	475.5	0.68
N-[(1S,2R)-1-benzyl-3-(cyclopropylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E450)	A73	C26	501.5	0.71

N-[(1S,2R)-3-(1-adamantylamino)-1-benzyl-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E451)	A73	C94	595.6	0.85
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-ylamino)propyl]-3-cyclopentyl-5-(2-oxopyrrolidin-1-yl)benzamide hydrochloride (E452)	A107	C95	566.5	0.91
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E453)	A73	C95	591.5	0.81
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(3-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E454)	A73	C96	595.6	0.79
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E455)	A73	C97	595.6	0.78
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-methoxyphenyl)ethyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E456)	A73	C98	595.4	0.79
N-((1S,2R)-1-benzyl-3-{[2-(2-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E457)	A73	C99	599.5	0.81
N-((1S,2R)-1-benzyl-3-{[2-(3-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E458)	A73	C100	599.5	0.82
N-((1S,2R)-1-benzyl-3-{[2-(4-chlorophenyl)ethyl]amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E459)	A73	C101	599.5	0.82
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(4-methylphenyl) ethyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E460)	A73	C102	579.5	2.02
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(2-methylphenyl) ethyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E461)	A73	C103	580.5	2.02
N-((1S,2R)-1-benzyl-3-{[2-(3,4-dichlorophenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E462)	A73	C104	633.4	2.15
N-((1S,2R)-1-benzyl-3-{[2-(2,4-dichlorophenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E463)	A73	C105	633.4	0.86

N-((1S,2R)-1-benzyl-3-{[2-(3,5-dimethoxyphenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E464)	A73	C106	625.5	0.8
N-((1S,2R)-1-benzyl-3-{[2-(2,3-dimethoxyphenyl)ethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E465)	A73	C107	625.4	0.79
N-[(1S,2R)-1-benzyl-3-(benzylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E466)	A73	C108	551.5	0.75
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(2-phenylethyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E467)	A73	C109	565.4	0.79
N-{(1S,2R)-1-benzyl-3-[(1-ethylcyclohexyl)amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E468)	A73	C110	571.6	0.82
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1-methylcyclopentyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E469)	A73	C111	544.5	1.81
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1-propylcyclopentyl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E470)	A73	C112	571.7	0.83
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1-propylcyclohexyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E471)	A73	C113	585.6	0.88
N-((1S,2R)-1-benzyl-3-{[2-(3-chlorophenyl)-1,1-dimethylethyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E472)	A73	C114	627.5	0.92
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(pyridin-3-ylmethyl)propyl] benzamide hydrochloride (E473)	A73	C115	582.0	1.75
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(1,3-thiazol-2-ylmethyl)propyl] benzamide hydrochloride (E474)	A73	C116	588.0	1.91
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E475)	A73	C117	550.0	1.88
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1,3-thiazol-2-ylmethyl)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E476)	A73	C118	580.1	2.21
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-{(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-[(3-methoxybenzyl)amino]	A73	C119	571.0	2.02

propyl}benzamide hydrochloride (E477)				
N-[(1S,2R)-3-(cyclohexylamino)-1-(2-furylmethyl)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E478)	A73	C120	533.0	2.01
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-1-(2-furylmethyl)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide hydrochloride (E479)	A73	C121	563.1	2.32
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-{(1S,2R)-1-(2-furylmethyl)-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}benzamide hydrochloride (E480)	A73	C122	577.2	2.39
3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-N-[(1S)-2-hydroxy-3-[(3-methoxybenzyl)amino]-1-(pyridin-2-ylmethyl)propyl] benzamide (E481)	A73	C123	581.9	1.84
N-[(1S,2R)-1-[(4-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E482)	A73	C124	577.4	0.82
N-[(1S,2R)-1-[(4-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E483)	A73	C125	615.4	0.82
3-cyclopentyl-N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide hydrochloride (E484)	A107	C126	630.4	0.94
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E485)	A73	C126	655.4	0.85
N-[(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E486)	A73	C127	617.3	0.8
N-{(1S,2R)-1-[(3,5-difluorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E487)	A73	C128	609.5	0.9
N-{(1S,2R)-3-(cyclohexylamino)-1-[(3,5-difluorophenyl)methyl]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E488)	A73	C129	579.4	0.8
N-{(1S,2R)-1-[(3,5-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E489)	A73	C130	623.6	0.93

N-[(1S,2R)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E490)	A73	C131	617.5	0.81
N-{(1S,2R)-3-(cyclohexylamino)-1-[(3,4-difluorophenyl)methyl]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E491)	A73	C132	579.5	0.79
N-{(1S,2R)-1-[(3,4-difluorophenyl)methyl]-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E492)	A73	C133	623.5	0.92
N-[(1S,2R)-1-[(3-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E493)	A73	C134	616.3	0.83
N-[(1S,2R)-1-[(3-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E494)	A73	C135	578.3	0.83
N-[(1S,2R)-1-[(2-chlorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E495)	A73	C136	616.4	0.86
N-[(1S,2R)-1-[(2-chlorophenyl)methyl]-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E496)	A73	C137	578.4	0.85
N-{(1S,2R)-1-[(2-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E497)	A73	C138	608.5	0.98
N-{(1S,2R)-1-[(3-chlorophenyl)methyl]-3-[(1,5-dimethylhexyl)amino]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E498)	A73	C139	608.5	1
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-1-[(3-fluorophenyl)methyl]-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)propyl]benzamide hydrochloride (E499)	A73	C140	599.4	0.82
N-{(1S,2R)-3-[(1,5-dimethylhexyl)amino]-1-[(3-fluorophenyl) methyl]-2-hydroxypropyl}-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E500)	A73	C141	591.6	0.95
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}	A73	C142	587.4	0.79

amino)-1-(2-thienylmethyl)propyl] benzamide hydrochloride (E501)				
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(2-thienylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E502)	A73	C143	579.5	0.92
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(1H-pyrazol-1-ylmethyl)propyl] benzamide hydrochloride (E503)	A73	C144	571.4	0.65
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(1H-pyrazol-1-ylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E504)	A73	C145	563.5	0.8
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl} amino)-1-(3-thienylmethyl)propyl] benzamide hydrochloride (E505)	A73	C146	587.5	0.76
N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(3-thienylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E506)	A73	C147	579.5	0.85
formic acid - N-{(1S,2R)-1-benzyl-3-[(1,1-dimethylhexyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E507)	A31	C48	523.3	2.76
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E508)	A31	C40	597.3	3.03
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-methyl-5-(trifluoromethyl)benzyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E509)	A73	C49	633.2	2.84
formic acid - N-{(1S,2R)-1-benzyl-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E510)	A73	C50	577.2	2.68
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E511)	A31	C51	543.1	2.55
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(6-methoxy-2,3-dihydro-1H-inden-1-yl)amino]propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E512)	A73	C52	607.5	2.55
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E513)	A73	C53	593.4	2.40
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(isobutylthio)-1,1-dimethylethyl]amino} propyl)-3-(ethylamino)-5-(2-	A31	C54	555.4	2.62

oxopyrrolidin-1-yl)benzamide (E514)				
N-{(1S,2R)-1-benzyl-3-[(1,1-dimethyl-2-phenoxyethyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E515)	A31	C55	559.4	2.56
N-((1S,2R)-1-benzyl-3-{[2-(benzyloxy)-1,1-dimethylethyl]amino}-2-hydroxypropyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E516)	A31	C56	573.5	2.58
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxyphenyl)amino] propyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E517)	A31	C57	517.4	2.92
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({2-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E518)	A31	C58	583.4	2.62
formic acid - N-{(1S,2R)-1-benzyl-3-[(1,1-dimethyl-2-phenylethyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E519)	A31	C59	543.5	2.55
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(1-naphthyl)ethyl]amino} propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E520)	A31	C60	565.5	2.63
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[2-(3-methoxyphenyl)-1,1-dimethylethyl]amino} propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E521)	A31	C61	573.5	2.57
N-[(1S,2R)-3-anilino-1-benzyl-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E522)	A31	C62	487.4	2.90
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl) cyclopropyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E523)	A31	C63	557.4	2.47
formic acid - N-{(1S,2R)-1-benzyl-3-[(cyclohexylmethyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E524)	A31	C64	507.5	2.48
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(tetrahydro-2H-pyran-4-ylmethyl)amino]propyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E525)	A31	C65	509.4	2.15
N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-thiopyran-4-ylamino)propyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E526)	A31	C66	511.4	2.30
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(isopropylamino)propyl]-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E527)	A141	C28	478.5	2.04
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E528)	A141	C1	517.5	2.17
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-	A141	C5	561.5	2.56

trimethylhexyl)amino] propyl}-3-ethyl-7-(2-oxopyrrolidin-1-yl)-1H-indole-5-carboxamide (1:1) (E529)				
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl}-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E530)	A144	C14	591.4	2.36
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (E531)	A144	C5	597.5	2.72
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E532)	A144	C1	554.5	2.33
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(isopropylamino)propyl]-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E533)	A144	C28	514.4	2.14
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl)-1-methylethyl]amino}propyl)-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E534)	A144	C15	619.4	2.45
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-7-(1,1-dioxidoisothiazolidin-2-yl)-3-ethyl-1H-indole-5-carboxamide (1:1) (E535)	A144	C40	657.4	2.62
N-[(1S,2R)-1-benzyl-3-(sec-butylamino)-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E536)	A31	C67	467.3	2.4
N-{(1S,2R)-1-benzyl-3-[(4-tert-butylcyclohexyl)amino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E537)	A31	C68	549.3	2.81
N-{(1S,2R)-1-benzyl-3-[(1S)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E538)	A31	C50	527.2	2.56
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(2-isobutoxy-1,1-dimethylethyl)amino] propyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E539)	A31	C70	539.2	2.64
N-[(1S,2R)-1-benzyl-3-({1,1-dimethyl-2-[(2-methylprop-2-en-1-yl)oxy]ethyl}amino)-2-hydroxypropyl]-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E540)	A31	C71	537.2	2.61
N-{(1S,2R)-1-benzyl-3-[(1R)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (E541)	A31	C72	527.2	2.54
N-{(1S,2R)-1-benzyl-3-[(1R)-2,3-dihydro-1H-inden-1-ylamino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (E542)	A73	C72	577.2	2.64

N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl}-3-[ethyl(methyl)amino]-5-(2-oxopyrrolidin-1-yl)benzamide (E543)	A128	C14	546.5	2.49
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl)-1-methylethyl]amino}propyl)-3-[ethyl(methyl)amino]-5-(2-oxopyrrolidin-1-yl)benzamide (E544)	A128	C15	574.5	2.58
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl) cyclohexyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E545)	A31	C41	599.5	2.60
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[1-(3-methoxyphenyl) cyclohexyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E546)	A73	C41	649.5	2.70
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E547)	A73	C42	555.3	2.35
formic acid - N-((1S,2R)-1-benzyl-2-hydroxy-3-{[(1-methyl-1H-pyrazol-4-yl)methyl]amino}propyl)-3-(ethylamino)-5-(2-oxopyrrolidin-1-yl)benzamide (1:1) (E548)	A31	C42	505.3	2.27
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E549)	A73	C1	543.4	2.45
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)benzamide (1:1) (E550)	A73	C43	545.4	2.28
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (1:1) (E551)	A126	C1	568.3	2.80
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-cyclopentyl-5-(1,1-dioxido-1,2-thiazinan-2-yl)benzamide (1:1) (E552)	A126	C43	570.3	2.61
formic acid - N-{(1S,2R)-1-benzyl-3-[(3,3-dimethylbutyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E553)	A119	C44	563.4	2.53
N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,3,3-tetramethylbutyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (E554)	A119	C45	591.4	2.63
formic acid - N-{(1S,2R)-1-benzyl-3-[(1,3-dimethylbutyl) amino]-2-hydroxypropyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E555)	A119	C46	563.4	2.50
formic acid - N-[(1S,2R)-1-benzyl-3-(cyclohexylamino)-2-hydroxypropyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E556)	A127	C1	557.4	2.35
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-	A127	C28	517.4	2.20

(isopropylamino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E557)				
formic acid - N-[(1S,2R)-1-benzyl-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)propyl]-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E558)	A127	C40	661.4	2.70
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(3-methoxybenzyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E559)	A127	C14	595.4	2.41
N-((1S,2R)-1-benzyl-2-hydroxy-3-{[3-(trifluoromethyl)benzyl] amino}propyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (E560)	A127	C16	633.4	2.66
formic acid - N-{(1S,2R)-1-benzyl-2-hydroxy-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(isopropylamino) benzamide (1:1) (E561)	A127	C5	601.5	2.80
formic acid - N-((1S,2R)-1-benzyl-3-{[4-fluoro-3-(trifluoromethyl)benzyl] amino}-2-hydroxypropyl)-3-(1,1-dioxido-1,2-thiazinan-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E562)	A119	C47	655.4	2.50
formic acid - 3-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-piperidinyl)benzamide (1:1) (E563)	A59	C14	545.2	2.79
formic acid - N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(ethylamino)-5-(2-oxo-1-piperidinyl)benzamide (1:1) (E564)	A59	C20	537.3	2.81
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-(2-oxo-1-piperidinyl)benzamide (E565)	A59	C16	583.2	2.69
formic acid - N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (1:1) (E566)	A116	C14	544.3	2.74
formic acid - N-[(1S,2R)-3-[(1,5-dimethylhexyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (1:1) (E567)	A116	C20	536.3	3.01
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (E568)	A116	C16	582.2	2.88
N-[(1S,2R)-3-{[(1S)-2-(cyclohexylamino)-1-methyl-2-oxoethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-1-piperidinyl)-5-propylbenzamide (E569)	A116	C6	577.3	2.76
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}benzamide (E570)	A70	C5	573.5	2.67

Examples 571-572 (E571-E572)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde:

Example	Precursor	[M+H]+	RT (min)
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-2-hydroxy-3-({[1-(1-methylethyl)-1*H*-pyrazol-4-yl]methyl}amino)-1-(phenylmethyl)propyl]benzamide (1:1) (E571)	D120	583.5	2.24
formic acid - 3-(1,1-dioxidotetrahydro-2*H*-1,2-thiazin-2-yl)-5-(ethylamino)-*N*-[(1*S*,2*R*)-2-hydroxy-1-(phenylmethyl)-3-({[1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl]methyl}amino)propyl] benzamide (1:1) (E572)	D120	623.4	2.28

Examples 573-695 (E573-E695)

Examples E573-695 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
formic acid - 5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (1:1) (E573)	A118	C14	549.3	2.42
3-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E574)	A11	C40	598.4	2.76
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E575)	A18	C40	634.3	2.78
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E576)	A73	C40	647.4	2.78
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E577)	A140	C40	621.4	2.75
3-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E578)	A11	C15	560.4	2.62
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-	A140	C15	583.4	2.61

(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E579)				
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E580)	A141	C40	621.4	2.81
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethyloxy)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E581)	A18	C15	596.5	2.58
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E582)	A141	C15	583.5	2.62
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl] benzamide (E583)	A119	C14	599.4	2.27
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl] benzamide (E584)	A119	C16	637.4	2.48
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E585)	A70	C40	633.3	2.73
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E586)	A70	C15	595.3	2.57
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino) propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E587)	A118	C16	587.3	2.60
2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E588)	A120	C14	548.3	2.64
2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E589)	A120	C16	586.3	2.79
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E590)	A121	C14	620.5	3.02
N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E591)	A121	C28	542.4	2.88
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(2-oxo-5-phenyl-1-piperidinyl)-5-propylbenzamide (E592)	A121	C1	582.6	2.99

5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl) propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E593)	A118	C40	615.3	2.61
5-(ethylamino)-2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(2-oxo-1-pyrrolidinyl)benzamide (E594)	A118	C5	555.4	2.71
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)-2-fluoro-3-(2-oxo-1-pyrrolidinyl)benzamide (E595)	A118	C1	511.3	2.25
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E596)	A118	C28	471.3	2.05
5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)benzamide (E597)	A118	C15	577.4	2.42
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}benzamide (E598)	A119	C5	605.4	2.87
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (E599)	A119	C1	561.4	2.42
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl] benzamide (E600)	A119	C28	521.3	2.20
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E601)	A153	C14	592.3	2.39
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indazole-6-carboxamide (E602)	A153	C16	630.3	2.58
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E603)	A153	C15	620.3	2.46
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E604)	A153	C40	658.3	2.65
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1H-indazole-6-carboxamide (E605)	A153	C5	598.5	2.47
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1H-indazole-6-carboxamide (E606)	A153	C1	554.4	2.08

4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-1H-indazole-6-carboxamide (E607)	A153	C28	514.4	1.91
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E608)	A142	C14	569.5	2.38
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy) phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E609)	A142	C15	597.5	2.45
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E610)	A142	C40	635.4	2.71
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-ethyl-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E611)	A142	C1	531.5	2.33
3-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E612)	A142	C5	575.4	2.80
3-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide formate salt (1:1) (E613)	A122	C5	591.5	2.60
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}benzamide (1:1) (E614)	A73	C5	587.6	2.61
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluorobenzamide (E615)	A122	C1	547.5	2.08
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E616)	A146	C14	605.5	2.49
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-1H-indole-5-carboxamide (E617)	A146	C16	643.4	2.68
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E618)	A146	C15	633.4	2.57
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl]	A146	C40	671.4	2.74

ethyl}amino)-1-(phenylmethyl)propyl]-1-methyl-1H-indole-5-carboxamide (E619)				
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1-methyl-1H-indole-5-carboxamide (E620)	A146	C5	611.5	2.84
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-1-methyl-1H-indole-5-carboxamide (E621)	A146	C1	567.5	2.46
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methyl-5-(2-oxo-1-pyrrolidinyl)benzamide (E622)	A129	C16	583.2	2.70
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E623)	A130	C16	619.2	2.77
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E624)	A131	C16	633.2	2.84
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)benzamide (E625)	A132	C16	649.2	2.82
3-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-(2-oxo-1-pyrrolidinyl)benzamide (E626)	A133	C16	599.2	2.71
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)benzamide (E627)	A134	C16	635.2	2.76
3-(diethylamino)-5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methylbenzamide (E628)	A135	C16	661.2	2.94
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-[(1E)-1-propen-1-yl]benzamide (E629)	A136	C16	646.1	2.95
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(methyloxy)-5-propylbenzamide (E630)	A137	C16	648.2	2.99
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E631)	A154	C16	565.2	2.59

1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E632)	A140	C16	593.2	2.83
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E633)	A140	C14	555.2	2.36
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E634)	A155	C14	577.1	2.31
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E635)	A147	C14	605.4	2.60
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(1-methylethyl)-5-(2-oxo-1-pyrrolidinyl)benzamide (E636)	A104	C14	530.5	2.60
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-1-methyl-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E637)	A156	C14	541.2	2.50
3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl) propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E638)	A138	C14	607.2	2.43
1-butyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E639)	A157	C14	583.2	2.78
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1-pentyl-1H-indole-6-carboxamide (E640)	A158	C14	597.2	2.90
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E641)	A122	C14	585.3	2.47
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl) phenyl] methyl}amino)propyl] benzamide (E642)	A122	C16	623.3	2.62
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E643)	A122	C15	613.3	2.56
3-(1,1-dioxido-2-isothiazolidinyl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E644)	A122	C40	651.3	2.70
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E645)	A119	C15	627.3	2.63

3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}amino)-1-(phenylmethyl)propyl] benzamide (E646)	A119	C40	665.3	2.77
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E647)	A143	C14	591.3	2.60
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-6-carboxamide (E648)	A143	C16	629.3	2.75
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E649)	A143	C15	619.4	2.67
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E650)	A143	C40	657.4	2.80
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-2-(methyloxy)benzamide (E651)	A139	C14	611.4	2.59
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-2-(methyloxy)benzamide (E652)	A139	C16	649.3	2.76
5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N'-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-N,N-dipropyl-1,3-benzenedicarboxamide (E653)	A95	C15	693.5	2.82
5-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N'-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-N,N-dipropyl-1,3-benzenedicarboxamide (E654)	A95	C40	731.4	2.94
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E655)	A152	C14	556.3	2.33
1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E656)	A152	C16	594.3	2.42
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E657)	A152	C15	584.4	2.42
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-	A152	C40	622.4	2.61

(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-indazole-6-carboxamide (E658)				
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-2,3-dihydro-1H-indole-6-carboxamide (E659)	A145	C14	607.4	2.61
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1H-indole-6-carboxamide (E660)	A147	C5	611.5	2.92
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-1H-indole-6-carboxamide (E661)	A143	C5	597.5	2.85
1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E662)	A140	C5	561.5	2.83
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-1H-indole-6-carboxamide (E663)	A147	C1	567.5	2.62
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-1H-indole-6-carboxamide (E664)	A143	C1	553.5	2.54
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1H-indole-6-carboxamide (E665)	A140	C1	517.4	2.51
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-6-carboxamide (E666)	A147	C16	643.5	2.86
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E667)	A147	C15	633.5	2.75
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-indole-6-carboxamide (E668)	A147	C40	671.5	2.92
7-[acetyl(ethyl)amino]-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino) propyl]-3-methyl-1-benzofuran-5-carboxamide (E669)	A159	C16	580.2	2.81
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-methyl-7-(2-	A160	C16	579.2	2.68

oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E670)				
N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E671)	A161	C16	607.2	2.85
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E672)	A162	C16	621.2	2.89
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-7-(2-oxo-1-pyrrolidinyl)-1-benzofuran-5-carboxamide (E673)	A163	C16	594.2	2.90
formic acid - N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-methyl-8-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2H-chromene-6-carboxamide (1:1) (E674)	A164	C16	596.2	2.81
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E675)	A141	C16	593.2	2.81
3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1-methyl-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E676)	A142	C16	607.2	2.83
7-(1,1-dioxido-2-isothiazolidinyl)-3-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-indole-5-carboxamide (E677)	A144	C16	629.1	2.87
N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-3-(1-methylethyl)-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (E678)	A161	C14	569.5	2.65
formic acid - 3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-pyrrolidinyl)-1H-indole-5-carboxamide (1:1) (E679)	A141	C14	555.1	2.44
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (1:1) (E680)	A149	C14	556.5	2.24
formic acid - 7-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-indole-5-carboxamide (1:1) (E681)	A148	C14	605.5	2.63
formic acid - 3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-1-piperidinyl)-1H-indole-5-carboxamide (1:1) (E682)	A165	C14	569.2	2.68

3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-nitrobenzamide (E683)	A123	C14	659.3	2.95
3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E684)	A125	C14	657.4	2.85
3-amino-5-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl] benzamide (E685)	A124	C14	629.4	2.67
3-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl] methyl}amino)-1-(phenylmethyl)propyl]-7-(2-oxo-4-phenyl-1-pyrrolidinyl)-1H-indole-5-carboxamide (E686)	A166	C14	631.4	2.92
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide (E687)	A125	C1	619.4	2.89
3-(1,1-dioxido-4-phenyltetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl] benzamide (E688)	A125	C28	579.4	2.76
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-1,2,3-benzotriazole-6-carboxamide (1:1) (E689)	A167	C16	595.3	2.67
formic acid - 4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (1:1) (E690)	A151	C14	606.3	2.21
1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E691)	A149	C16	594.5	2.21
1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E692)	A149	C40	622.5	2.24
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-1-ethyl-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E693)	A149	C1	518.4	1.90
1-ethyl-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-4-(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (E694)	A149	C5	562.5	2.33
formic acid - 1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl}amino)-1-(phenylmethyl)propyl]-4-	A149	C15	584.5	2.09

(2-oxo-1-pyrrolidinyl)-1H-benzimidazole-6-carboxamide (1:1) (E695)				

Example 696

3-(1,1-dioxidotetrahydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E696)

Example 696 was prepared from Description 313 in an analogous manner to that described for Example 213. $[M+H]^+$ = 594.4, RT = 2.77 min

Example 697

3-(1,1-dioxidotetrahydro-1,2-thiazepin-2(3H)-yl)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl]methyl}amino)propyl]-5-propylbenzamide (E697)

Example 697 was prepared from Description 312 in an analogous manner to that described for Example 213. $[M+H]^+$ = 632.1, RT = 3.00 min

Examples 698-703 (E698-703)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
N-[(1S,2R)-3-{[2-(3-chlorophenyl)-1-methylethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E698)	D120	611.3	1.01
N-[(1S,2R)-3-{[2-(3-chlorophenyl)-1-methylethyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-3-cyclopentyl-5-(1,1-dioxido tetrahydro-2H-1,2-thiazin-2-yl)benzamide hydrochloride (E699)	D125	638.4	1.00
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-{[(5-ethyl-3-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E700)	D120	585.5	2.57
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-{[(4-ethyl-2-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E701)	D120	585.5	2.45
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-3-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E702)	D120	569.5	2.31
formic acid – 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-((1S,2R)-2-hydroxy-1-(phenylmethyl)-3-{[(1-propyl-1H-pyrazol-4-yl)methyl]amino}propyl) benzamide (1:1) (E703)	D120	583.5	2.29

Example 704

Example E704 was prepared in an analogous manner to Example 1 from the appropriate acid and amine indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
N-[(1S,2R)-3-(bicyclo[2.2.2]oct-1-ylamino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E704)	A73	C153	569.5	2.02

Examples 705-709 (E705-709)

The following compounds were prepared in an analogous manner to Example 183 from the appropriate amine and the appropriate aldehyde or ketone :

Example	Precursor	$[M+H]^+$	RT (min)
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-{[(5-ethenyl-3-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E705)	D120	583.5	2.55
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-{[(4-ethenyl-2-furanyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E706)	D120	567.5	2.44
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[1-(2-propen-1-yl)-1H-pyrazol-4-yl]methyl}amino)propyl] benzamide (1:1) (E707)	D120	581.5	2.29
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-{[(4-ethenyl-2-thienyl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(ethylamino)benzamide (1:1) (E708)	D120	583.5	2.52
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-({[1-(2-fluoroethyl)-1H-pyrazol-4-yl]methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl] benzamide (1:1) (E709)	D120	587.5	2.22

Examples 710-744 (E710-744)

Examples E710-E744 were prepared in an analogous manner to Example 1 from the appropriate acid and amines indicated in the below table:

Example	Acid	Amine	$[M+H]^+$	RT (min)
3-cyclopentyl-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-(2-oxo-1-pyrrolidinyl)benzamide (E710)	A107	C154	544.7	2.51
3-(ethyloxy)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-	A11	C154	520.7	2.20

(2-oxo-1-pyrrolidinyl)benzamide (E711)				
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl] benzamide (E712)	A73	C154	569.6	2.19
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-5-propylbenzamide (E713)	A112	C154	568.6	2.46
formic acid - N-[(1S,2R)-3-[(4,4-difluorocyclohexyl)amino]-2-hydroxy-1-(phenylmethyl) propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluorobenzamide (1:1) (E714)	A119	C155	597.4	2.30
4-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-8-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E715)	A171	C14	572.5	2.61
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (E716)	A150	C14	592.4	2.21
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1H-benzimidazole-6-carboxamide (E717)	A150	C16	630.4	2.51
4-(1,1-dioxido-2-isothiazolidinyl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-1H-benzimidazole-6-carboxamide (E718)	A150	C40	658.4	2.51
4-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-1-ethyl-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl) phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-2,3-dihydro-1H-indole-6-carboxamide (E719)	A145	C40	673.5	2.90
8-(1,1-dioxido-2-isothiazolidinyl)-4-ethyl-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-1,2,3,4-tetrahydro-6-quinoxalinecarboxamide (E720)	A172	C16	646.5	2.65
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[({3-[(trifluoromethyl)oxy] phenyl}methyl)amino] propyl}benzamide (1:1) (E721)	A119	C11	653.5	2.54
formic acid - 3-(1,1-dioxido-2-isothiazolidinyl)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-	A174	C154	572.4	2.37

propylbenzamide (1:1) (E722)				
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-5-propylbenzamide (E723)	A174	C5	590.5	2.92
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl} amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E724)	A174	C15	612.5	2.66
3-(1,1-dioxido-2-isothiazolidinyl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (E725)	A174	C16	622.4	2.68
N-[(1S,2R)-3-[(1r,4R)-bicyclo[2.2.1]hept-1-ylamino]-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E726)	A73	C152	555.1	2.23
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-5-propylbenzamide (1:1) (E727)	A173	C154	586.4	2.50
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-5-propylbenzamide (E728)	A173	C43	562.4	2.45
formic acid - 3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (1:1) (E729)	A173	C40	664.5	2.97
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-({[3-(trifluoromethyl)phenyl] methyl}amino)propyl]-5-propylbenzamide (E730)	A173	C16	636.4	2.84
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-2-fluoro-N-[(1S,2R)-2-hydroxy-3-({[3-(methyloxy)phenyl]methyl}amino)-1-(phenylmethyl)propyl]-5-propylbenzamide (E731)	A173	C14	598.4	2.70
2-fluoro-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tetrahydro-2H-pyran-4-ylamino)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E732)	A120	C43	512.5	2.32
N-[(1S,2R)-3-{[(1-ethyl-1H-pyrazol-4-yl)methyl]amino}-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E733)	A120	C154	536.5	2.36
N-[(1S,2R)-3-({[3,4-bis(methyloxy)phenyl] methyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E734)	A120	C156	578.5	2.40

2-fluoro-N-[(1S,2R)-2-hydroxy-3-[(1-methylethyl)amino]-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E735)	A120	C28	470.5	2.26
N-[(1S,2R)-3-(cyclohexylamino)-2-hydroxy-1-(phenylmethyl)propyl]-2-fluoro-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (E736)	A120	C1	510.5	2.44
formic acid - 2-fluoro-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1,1,5-trimethylhexyl)amino] propyl}-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E737)	A120	C5	554.7	3.04
formic acid - 2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(trifluoromethyl)phenyl] ethyl}amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E738)	A120	C40	614.6	2.77
formic acid - 2-fluoro-N-[(1S,2R)-2-hydroxy-3-({1-methyl-1-[3-(methyloxy)phenyl]ethyl} amino)-1-(phenylmethyl)propyl]-3-(2-oxo-1-pyrrolidinyl)-5-propylbenzamide (1:1) (E739)	A120	C15	576.6	2.66
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-3-[(1-ethylcyclobutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl] benzamide hydrochloride (E740)	A73	C69	542.9	1.05
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-{(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-[(1-propylcyclobutyl)amino] propyl}benzamide hydrochloride (E741)	A73	C148	556.9	1.08
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-3-{[1-(1-methylethyl)cyclobutyl] amino}-1-(phenylmethyl)propyl] benzamide hydrochloride (E742)	A73	C149	556.9	1.07
N-[(1S,2R)-3-({1-[(3-chlorophenyl)methyl] cyclobutyl}amino)-2-hydroxy-1-(phenylmethyl)propyl]-3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)benzamide hydrochloride (E743)	A73	C150	639.3	1.41
3-(1,1-dioxidotetrahydro-2H-1,2-thiazin-2-yl)-5-(ethylamino)-N-[(1S,2R)-2-hydroxy-1-(phenylmethyl)-3-(tricyclo[3.3.1.1~3,7~]dec-2-ylamino)propyl] benzamide hydrochloride (E744)	A73	C151	595.7	2.12

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) **Asp-2 inhibitory assay**

For each compound being assayed, in a 384 well plate, is added:-

a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).
b) 10 μl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid). Aminomethyl fluorescein (FAM) and tetramethyl rhodamine (TAMRA) are fluorescent molecules which co-operate to emit fluorescence at 535nm upon cleavage of the SEVNLDAEFK peptide.
c) 10 μl enzyme solution. This is prepared by diluting 16ml of a 500nM enzyme solution into 384 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

(II) Cathepsin D inhibitory assay

For each compound being assayed, in a 384 well plate, is added:-
a) 1μl of a DMSO solution of the test compound (IC_{50} curve uses ten 1 in 2 serial dilutions from 500 μM).
b) 10 μl of substrate (FAM-SEVNLDAEFK-TAMRA) solution in buffer. This is prepared by diluting 2ml of a 2mM DMSO solution of the substrate into 400ml of buffer (100mM Sodium acetate pH = 4.5, 1 l Milli-Q water, 0.06% Triton X-100 (0.5 ml/l) , pH adjusted to 4.5 using glacial acetic acid).
c) 10 μl enzyme solution. This is prepared by diluting 1.6ml of a 200 unit/ml (in 10 mM HCl) enzyme solution into 398.4 ml of buffer (prepared as above).
Blank wells (enzyme solution replaced by buffer) are included as controls on each plate. Wells are incubated for 1h at room temperature and fluorescence read using a Tecan Ultra Fluorimeter/Spectrophotometer (485nm excitation, 535nm emission).

Pharmacological Data

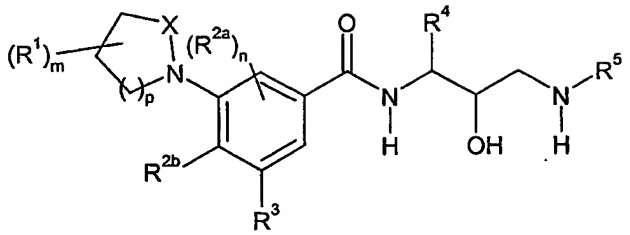
The compounds of E1-E744 were tested in Assays (I) and (II) and exhibited inhibition within the following range: 1-10000 nM (Asp-2) and 10-10000 nM (CatD). More particularly, the compounds of E12, 22, 30, 31, 33, 50, 54-56, 60, 65, 86, 102, 179, 218, 222-223, 241, 245-246, 249, 255, 266, 270, 271, 277-278, 280-289, 296, 299, 303, 313-315, 317-318, 320-322, 325, 327, 329, 332-333, 361-363, 373, 375, 406-408, 559-560, 562, 583-584, 587, 632, 641-642, 647-648, 656, 680, 690-691, 694-695, 700, 703, 708, 713, 716-718, 720-721, 725, 727, 730-731 and 733 exhibited inhibition within the following range: 1-50 nM (Asp-2) and 100-10000 nM (CatD). Yet more particularly, the compounds of E30-31, 33, 270, 562, 584, 700 and 721 exhibited inhibition within the following range: 1-10 nM (Asp-2) and 500-10000 nM (CatD).

Abbreviations

DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMAP	dimethylaminophenol
DABCO	1,4-diazabicyclo [2.2.2] octane
DME	dimethyl ether
EDAC	N-ethyl-N-(3-dimethylamino propyl)carbodiimide
THF	tetrahydrofuran
DEAD	diethylacetylene dicarboxylate
DCM	dichloromethane
TFA	trifluoroacetic acid
HOBT	N-hydroxybenzotriazole
FAM	carboxyfluorescein
TAMRA	carboxytetramethylrhodamine
[ ]	single amino acid letter code relating to peptide sequence

Claims

1. A compound of formula (I):



(I)

wherein

R^1 represents C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^{2a} represents hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy or halogen;

m and n independently represent 0, 1 or 2;

X represents CO, SO or SO_2;

p represents an integer from 1 to 3;

R^{2b} represents hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, halogen, C_{1-6} alkoxy, amino, cyano, hydroxy, aryl, heteroaryl or heterocyclyl;

R^3 represents halogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -C_{2-6} alkenyl-aryl, -C_{2-6} alkenyl-heteroaryl, -C_{2-6} alkenyl-heterocyclyl, C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, cyano, azido, nitro, $-NR^7R^8$, -NR^9COR^{10}, -$NR^{11}SO_2R^{12}$, -OR^{13}, -SO_2R^{14}, -SR^{15}, -$C{\equiv}CR^{16}$, -C_{1-6} alkyl-$(CF_2)_qCF_3$, -$CONR^{17}R^{18}$, $COOR^{19}$, -C_{1-6} alkyl-$NR^{20}R^{21}$ or -C_{1-6} alkyl-N_3, or R^3 and R^{2b} together with the phenyl group to which they are attached form a naphthyl or benzofused heterocyclic or heteroaryl ring optionally substituted by one or two C_{1-6} alkyl groups;

R^4 represents –C_{2-6} alkynyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl;

R^5 represents hydrogen, -C_{1-10} alkyl, -C_{3-10} cycloalkyl, -C_{3-10} cycloalkenyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-10} cycloalkyl, -C_{3-10} cycloalkyl-C_{1-10} alkyl, -C_{3-10} cycloalkyl-C_{1-6} alkyl-aryl, -C_{3-10} cycloalkyl-aryl, -C_{1-6} alkyl-aryl-heteroaryl, -$C(R^aR^b)$-CONH-C_{1-6} alkyl, -$C(R^cR^d)$-CONH-C_{3-10} cycloalkyl, -C_{1-6} alkyl-S-C_{1-6} alkyl, -C_{1-6} alkyl-NR^eR^f, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl -C_{1-6} alkyl-C_{1-6} alkoxy-aryl, -C_{1-6} alkyl-C_{1-6} alkoxy-heteroaryl or -C_{1-6} alkyl-C_{1-6} alkoxy-heterocyclyl;

R^7, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} cycloalkyl, aryl, heteroaryl, heterocyclyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl or -CO-C_{1-6} alkyl;

R^{11}, R^{12}, R^a, R^c, R^e and R^f independently represent hydrogen, C_{1-6} alkyl or C_{3-8} cycloalkyl;

R^b and R^d independently represent hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl or -C_{1-6} alkyl-SO_2-C_{1-6} alkyl;

q represents 1 to 3;

wherein said alkyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenoxy, C_{3-8} cycloalkyl, amino, cyano or hydroxy groups;

and wherein said cycloalkyl, aryl, heteroaryl or heterocyclyl groups may be optionally substituted by one or more (eg. 1, 2 or 3) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, haloC_{1-6} alkyl, $-OCF_3$, oxo, C_{1-6} alkoxy, $-C_{1-6}$ alkoxy-CN, amino, cyano, nitro, $-NR^{22}COR^{23}$, $-CONR^{22}R^{23}$, $-COOR^{22}$, $-SO_2R^{22}$, $-C_{1-6}$ alkyl-NR^{22} R^{23} (wherein R^{22} and R^{23} independently represent hydrogen or C_{1-6} alkyl), $-C_{1-6}$ alkyl-C_{1-6} alkoxy, $-C_{1-6}$ alkanol or hydroxy groups;
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 which is a compound of formula E1-E744 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

4. A compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use as a pharmaceutical.

5. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

6. Use of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

7. A method of treatment or prophylaxis of diseases characterised by elevated β-amyloid levels or β-amyloid deposits which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof.

8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of diseases characterised by elevated β-amyloid levels or β-amyloid deposits.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/26 C07D279/02 C07D417/12 C07D405/12 C07D409/12
C07D403/12 C07D401/12 C07D275/02 C07D211/76 A61K31/4015
A61K31/45 A61K31/415 A61K31/541 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 02512 A (UPJOHN CO ;ELAN PHARM INC (US)) 10 January 2002 (2002-01-10) cited in the application claims 1,218-255	1,3
A	WO 02 02505 A (ELAN PHARM INC) 10 January 2002 (2002-01-10) cited in the application claims 1,39-85	1,3
A	WO 98 33795 A (ELLMAN JONATHAN A ;SKILLMAN A GEOFFREY (US); KUNTZ IRWIN D (US); R) 6 August 1998 (1998-08-06) claims 1,11,12 page 7, line 14 - line 26	1,3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 March 2004	13/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/13806

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/13806

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International Application No
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